Clinical trial results:
Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients 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	2013-003205-25
Trial protocol	DE AT NO ES BE Outside EU/EEA IT
Global end of trial date	17 November 2022

Results information

Result version number	v1 (current)
This version publication date	02 June 2023
First version publication date	02 June 2023

Trial information

Trial identification

Sponsor protocol code	CCTL019B2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02435849
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001654-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of tisagenlecleucel therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after tisagenlecleucel administration, which includes complete remission (CR) and CR with incomplete blood count recovery (CRi) as determined by Independent Review Committee (IRC) assessment.

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	08 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 1

Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United States: 39
Worldwide total number of subjects	80
EEA total number of subjects	28

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)	41
Adolescents (12-17 years)	25
Adults (18-64 years)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

98 patients were enrolled & 80 patients were infused in this study: 79 in the Main Cohort and 1 in Cohort 1. No patients were infused in Cohort 2. "Enrolled" means all eligibility criteria were met & apheresis was accepted by the manufacturing facility. Patients could discontinue the trial after enrollment and prior to tisagenlecleucel infusion.

Pre-assignment

Screening details:

This study was conducted in 11 countries with 23 sites.

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	Single dose of CTL019

Arm description:

Pediatric patients with relapsed or refractory B-cell ALL who were treated with single dose of tisagenlecleucel (CTL019).

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

Dosage and administration details:

A target per-protocol dose of CTL019 transduced cells consisting of a single infusion of 2.0 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 1.0 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). The following cell dose ranges was infused if all other safety release criteria are met: 0.2 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg).

Number of subjects in period 1	Single dose of CTL019
Started	80
Enrolled and infused	80
Enrolled but not infused	18 [1]
Discontinued study follow-up	49
Completed	31
Not completed	49
Adverse event, serious fatal	23
Physician decision	1
Lost to follow-up	1

New therapy for study indication	8
Subject/guardian decision	6
Lack of efficacy	10

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number is explaining the participants who entered the study but were not infused - a requirement to be considered as truly participating in the study.

Baseline characteristics

Reporting groups	
Reporting group title	Single dose of CTL019
Reporting group description:	
Pediatric patients with relapsed or refractory B-cell ALL who were treated with single dose of tisagenlecleucel (CTL019).	

Reporting group values	Single dose of CTL019	Total	
Number of subjects	80	80	
Age categorical Units: Subjects			
Children (2-11 years)	41	41	
Adolescents (12-17 years)	25	25	
Adults (18-64 years)	14	14	
Age Continuous Units: Years			
arithmetic mean	11.9		
standard deviation	± 5.42	-	
Sex: Female, Male Units: Participants			
Female	34	34	
Male	46	46	

End points

End points reporting groups

Reporting group title	Single dose of CTL019

Reporting group description:

Pediatric patients with relapsed or refractory B-cell ALL who were treated with single dose of tisagenlecleucel (CTL019).

Primary: Percentage of participants with Overall remission rate (ORR) as determined by Independent Review Committee (IRC) assessment.

End point title	Percentage of participants with Overall remission rate (ORR) as determined by Independent Review Committee (IRC) assessment.[1]

End point description:

Evaluating the efficacy of tisagenlecleucel therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after tisagenlecleucel administration. ORR included complete response (CR) and CR with incomplete blood count recovery (CRi) as determined by an Independent Review Committee (IRC) assessment.

End point type	Primary

End point timeframe:

during the 3 months after tisagenlecleucel administration

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: There is a statistical analysis done comparing the one group to fixed values of threshold, but the EudraCT system gave an error message when this was presented, stating that there has to be at least 2 comparison groups for a statistical analysis to be provided. So, the statistical analysis was removed.

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of participants				
number (confidence interval 95%)	82.3 (72.1 to 90.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Overall remission rate (ORR) from US manufacturing facilities (Key Secondary)

End point title	Percentage of participants with Overall remission rate (ORR) from US manufacturing facilities (Key Secondary)

End point description:

These are the percentage of participants with ORR who achieved overall remission rate which includes complete response (CR) and CR with incomplete blood count recovery (CRi) as determined by IRC assessment after having been infused with tisagenlecleucel from US manufacturing facilities.

End point type	Secondary

End point timeframe:

3 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percentage of participants				
number (confidence interval 95%)	82.1 (70.8 to 90.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Best Overall Response (BOR) of CR or CRi with minimal residue disease (MRD) negative bone marrow from US manufacturing facility as per IRC (Key Secondary)

End point title	Percentage of participants with Best Overall Response (BOR) of CR or CRi with minimal residue disease (MRD) negative bone marrow from US manufacturing facility as per IRC (Key Secondary)

End point description:

These are the percentage of participants who achieved Best Overall Response (BOR) of complete response (CR) or complete response with incomplete blood count recovery (CRi) with an MRD-negative bone marrow by central analysis using flow cytometry among participants who received tisagenlecleucel from US manufacturing facilities only, by IRC assessment.

End point type	Secondary

End point timeframe:

3 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percentage of participants				
number (confidence interval 95%)	82.1 (70.8 to 90.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Best Overall Response (BOR) of CR or CRi with MRD negative bone marrow by flow cytometry from all manufacturing

facilities as per IRC (Key Secondary)

End point title	Percentage of participants with Best Overall Response (BOR) of CR or CRi with MRD negative bone marrow by flow cytometry from all manufacturing facilities as per IRC (Key Secondary)

End point description:

These are the percentage of participants who achieved Best Overall Response (BOR) of CR or CRi with an MRD-negative bone marrow by central analysis using flow cytometry among participants who received tisagenlecleucel from all manufacturing facilities by IRC assessment. MRD negative = MRD% < 0.01%

End point type	Secondary

End point timeframe:

3 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of participants				
number (confidence interval 95%)	81.0 (70.6 to 89.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved CR or CRi and then proceeded to Hematopoietic Stem Cell Transplantation (HSCT) while in remission prior to month 6 resoonse

End point title	Percentage of participants who achieved CR or CRi and then proceeded to Hematopoietic Stem Cell Transplantation (HSCT) while in remission prior to month 6 resoonse

End point description:

These are the participants who achieved CR or CRi and then proceeded to HSCT while in remission prior to Month 6 response assessment

End point type	Secondary

End point timeframe:

6 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of Participants				
number (confidence interval 95%)	7.6 (2.8 to 15.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved CR or CRi without Hematopoietic Stem Cell Transplantation (HSCT)

End point title	Percentage of participants who achieved CR or CRi without Hematopoietic Stem Cell Transplantation (HSCT)

End point description:

These are the participants who achieved CR or CRi without HSCT between tisagenlecleucel (CTL019) infusion and Month 6 response assessment.

End point type	Secondary

End point timeframe:

6 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of participants				
number (confidence interval 95%)	60.8 (49.1 to 71.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who proceeded to Hematopoietic Stem Cell Transplantation (HSCT) after tisagenlecleucel (CTL019) infusion

End point title	Number of participants who proceeded to Hematopoietic Stem Cell Transplantation (HSCT) after tisagenlecleucel (CTL019) infusion

End point description:

These are the participants who achieved CR or CRi and then proceeded to SCT after being infused by tisagenlecleucel.

End point type	Secondary

End point timeframe:

up to 6 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Participants	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of remission (DOR)

End point title	Duration of remission (DOR)

End point description:

DOR is the time from achievment of CR or CRi, whichever occurs first, to relapse or death.

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: months				
median (confidence interval 95%)	46.8 (17.8 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Site of involvement of subsequent relapse

End point title	Site of involvement of subsequent relapse

End point description:

Anatomical location of relapse in participants who achieved prior CR/CRi subsequent to tisagenlecleucel infusion.

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants				
BM and/or blood relapse	23			
Extramedullary only	2			
Unknown	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free survival per IRC assessment

End point title	Relapse-free survival per IRC assessment

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

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: months				
median (confidence interval 95%)	46.8 (17.8 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival per IRC assessment

End point title	Event-free survival per IRC assessment

End point description:

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

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: months				
median (confidence interval 95%)	23.7 (9.2 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

OS, is the time from date of tisagenlecleucel infusion to the date of death due to any reason.

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: months				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants attaining CR or CRi at Day 28 +/- 4 days post tisagenlecleucel (CTL019) infusion by IRC assessment

End point title	Percentage of participants attaining CR or CRi at Day 28 +/- 4 days post tisagenlecleucel (CTL019) infusion by IRC assessment

End point description:

These are participants who had a day 28 response (CR or CRi response) by IRC assessment.

End point type	Secondary

End point timeframe:

1 month

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of participants				
number (confidence interval 95%)	78.5 (67.8 to 86.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response as a function of baseline tumor burden (tumor load)

End point title	Response as a function of baseline tumor burden (tumor load)

End point description:

Percentage of participants who achieved BOR of CR or CRi by flow cytometry as a function of baseline bone marrow tumor burden.

End point type	Secondary

End point timeframe:

3 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Percentage of participants				
number (confidence interval 95%)				
BL bone marrow tumor burden: Low (<50%) (n = 25)	96.0 (79.6 to 99.9)			
BL bone marrow tumor burden: High (>=50%)	75.9 (62.4 to 86.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bone marrow MRD status by flow cytometry per IRC assessment

End point title	Bone marrow MRD status by flow cytometry per IRC assessment

End point description:

Percentage of participants who achieved CR or CRi response with bone marrow MRD negative (MRD < 0.01%) after tisagenlecleucel infusion by flow cytometry.

End point type	Secondary

End point timeframe:

28 days

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of participants				
number (confidence interval 95%)	75.9 (65.0 to 84.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tisagenlecleucel transgene levels by qPCR, by day 28 disease response in blood, bone marrow and cerebrospinal fluid (CSF) if available, per IRC

End point title	Tisagenlecleucel transgene levels by qPCR, by day 28 disease response in blood, bone marrow and cerebrospinal fluid (CSF) if available, per IRC

End point description:

This is the summary of cellular kinetic concentrations for Tisagenlecleucel (CTL019) transgene levels by qPCR, by day 28 disease response by IRC assessment. No CSF samples were available.

End point type	Secondary

End point timeframe:

Month 60 (peripheral blood), Month 6 (bone marrow)

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: copies/ug DNA				
geometric mean (geometric coefficient of variation)				
M60: PB CTL019 Transgene: All participants (n= 20) M6: BM CTL019 Transgene: All Participants (n=39)	207 (± 95.5) 210 (± 138.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expression of tisagenlecleucel (CTL019) detected by flow cytometry in blood and bone marrow

End point title	Expression of tisagenlecleucel (CTL019) detected by flow cytometry in blood and bone marrow

End point description:

This is the summary cellular kinetic concentrations for CTL019 by flow cytometry, by day 28 disease response by IRC. It evaluated the persistence of transduced CTL019 cells post-infusion. Observation was up to Month 6 for bone marrow and up to Month 60 for peripheral blood.

End point type	Secondary

End point timeframe:

Month 60 (peripheral blood) Month 6 (bone marrow)

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of CD3+/CTL019+				
geometric mean (geometric coefficient of variation)				
M60: PB CD3+/CTL019+: All participants (n = 17) M6: BM CD3+/CTL019+: All participants (n = 49)	0.253 (± 67.4) 0.519 (± 185.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameter: Cmax by qPCR in peripheral blood, by Day 28 disease response by IRC

End point title	Pharmacokinetics (PK) parameter: Cmax by qPCR in peripheral blood, by Day 28 disease response by IRC

End point description:

Cmax is the maximum (peak) observed in peripheral blood drug concentration after single dose administration reported by CR/CRi, no response (NR), Unknown and by All participants.

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: copies/ug				
geometric mean (geometric coefficient of variation)				
CR/CRi (n = 62) NR (n = 5) Unknown (n = 8)	37200 (± 154.2) 31700 (± 87.4) 67700 (± 132.5)			

All Participants (n = 75)	39200 (± 148.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameter: Tmax by qPCR in peripheral blood, by Day 28 disease response by IRC

End point title	Pharmacokinetics (PK) parameter: Tmax by qPCR in peripheral blood, by Day 28 disease response by IRC

End point description:

Tmax is the time to reach maximum (peak) peripheral blood drug concentration after single dose administration (days)", reported by CR/CRi, no response (NR), Unknown and by All participants.

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: days				
median (full range (min-max))				
CR/CRi (n = 62)	9.87 (5.70 to 27.8)			
NR (n = 5)	20.9 (12.6 to 62.7)			
Unknown (n = 8)	13.4 (8.73 to 19.9)			
All Participants (n = 75)	9.98 (5.70 to 62.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameter: AUCs by qPCR in peripheral blood, by Day 28 disease response by IRC

End point title	Pharmacokinetics (PK) parameter: AUCs by qPCR in peripheral blood, by Day 28 disease response by IRC

End point description:

Tmax is the AUC from day of infusion to day 28 and 84 or other disease assessment days, in peripheral blood (% or copies/µg x days), reported by CR/CRi, no response (NR), Unknown and by All participants.

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: copies/ug*days				
geometric mean (geometric coefficient of variation)				
AUC0-28d: CR/CRi (n = 62)	310000 (± 192.2)			
AUC0-28d: NR (n = 5)	301000 (± 116.9)			
AUC0-28d: Unknown (n = 8)	768000 (± 177.4)			
AUC0-28d: All Participants	341000 (± 190.9)			
AUC 0-84d: CR/CRi (n = 56)	462000 (± 230.1)			
AUC 0-84d: NR (n = 3)	1130000 (± 75.5)			
AUC 0-84d: Unknown (n =7)	984000 (± 202.4)			
AUC 0-84d: All Participants (n = 66)	521000 (± 225.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Persistence of tisagenlecleucel (CTL019) in blood, bone marrow and CSF if available, by qPCR, by Day 28 response by IRC

End point title	Persistence of tisagenlecleucel (CTL019) in blood, bone marrow and CSF if available, by qPCR, by Day 28 response by IRC

End point description:

Persistence is defined as the time corresponding to last quantifiable transgene level in peripheral blood (Tlast), reported by CR/CRi, no response (NR), Unknown and by All participants.

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: days				
median (full range (min-max))				
Tlast CR/CRi (n = 62)	232 (19.8 to 1860)			
Tlast NR (n =6)	48.5 (13.9 to 888)			
Tlast Unknown (n= 8)	220 (64.0 to 1460)			
Tlast All Participants (n = 76)	179 (13.9 to 1860)			

Statistical analyses

No statistical analyses for this end point

Secondary: Prevalence and incidence of immunogenicity to tisagenlecleucel (CTL019)

End point title	Prevalence and incidence of immunogenicity to tisagenlecleucel (CTL019)

End point description:

This is defined as the percentage of participants who tested positive for anti-mCAR19 antibodies at any time post-baseline, reported by CR/CRi, no response (NR), Unknown and by All participants. .

End point type	Secondary

End point timeframe:

At any time post-baseline, up to a max. of 60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Participants				
CR/CRi positive	61			
NR positive	6			
Unknown positive	11			
All Patients positive	78			

Statistical analyses

No statistical analyses for this end point

Secondary: Effects of CTL019 therapy on Patient Reported Outcomes as measured by PedsQL questionnaire

End point title	Effects of CTL019 therapy on Patient Reported Outcomes as

	measured by PedsQL questionnaire

End point description:

The PedsQL questionnaire was for patients ≥ 8-years-old who achieved BOR as CR or CRi within 3 months and the questionnaire was on emotional, social, school, physical, and psychosocial health. Scores are transformed on a scale from 0 to 100, with the sum of all the items over the number of items answered on all the scales. Higher scores on the PedsQL questionnaire for these subscales indicate consistent improvement of health-related quality of life (HRQol).

End point type	Secondary

End point timeframe:

Month 3, M6, M12, M24, M60

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Scores on a scale				
arithmetic mean (standard error)				
M3 change from baseline - Emotional (n= 39)	14.5 (± 17.98)			
M6 change from baseline - Emotional (n = 37)	15.9 (± 18.96)			
M12 change from baseline - Emotional (n = 23)	24.6 (± 23.74)			
M24 change from baseline - Emotional (n = 20)	27.02 (± 21.85)			
M60 change from baseline - Emotional (n = 14)	21.4 (± 24.53)			
M3 change from baseline - Social (n = 39)	7.6 (± 13.90)			
M6 change from baseline - Social (n=37)	8.4 (± 17.04)			
M12 change from baseline - Social (n = 23)	14.8 (± 16.68)			
M24 change from baseline - Social (n = 20)	17.3 (± 15.85)			
M60 change from baseline - Social (n = 14)	17.9 (± 14.77)			
M3 change from baseline - School (n = 30)	8.9 (± 14.35)			
M6 change from baseline - School (n = 29)	10.0 (± 16.58)			
M12 change from baseline - School (n = 20)	19.0 (± 19.97)			
M24 change from baseline - School (n = 18)	13.9 (± 23.98)			
M60 change from baseline - School (n = 13)	17.7 (± 24.46)			
M3 change from baseline - Physical (n = 39)	17.5 (± 18.36)			
M6 change from baseline - Physical (n = 37)	21.6 (± 25.81)			
M12 change from baseline - Physical (n = 23)	31.1 (± 28.57)			
M24 change from baseline - Physical (n = 20)	37.4 (± 25.12)			
M60 change from baseline - Physical (n = 14)	37.1 (± 24.90)			

M3 change from BL - Psychosocial health (n = 39)	10.4 (± 12.38)			
M6 change from BL - Psychosocial health (n = 37)	11.0 (± 14.08)			
M12 change from BL - Psychosocial health (n = 23)	19.8 (± 16.80)			
M24 change from BL - Psychosocial health (n = 20)	20.1 (± 16.34)			
M60 change from BL - Psychosocial health (n = 14)	18.9 (± 15.15)			
M3 change from baseline - Total score (n = 39)	13.0 (± 13.28)			
M6 change from baseline - Total score (n = 37)	14.8 (± 17.00)			
M12 change from baseline - Total score (n = 23)	2.8 (± 19.56)			
M24 change from baseline - Total score (n = 20)	26.2 (± 16.70)			
M60 change from baseline - Total score (n = 14)	25.3 (± 15.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effects of CTL019 therapy on Patient Reported Outcomes as measured by EQ-5D questionnaire

End point title	Effects of CTL019 therapy on Patient Reported Outcomes as measured by EQ-5D questionnaire

End point description:

Results from the EQ-5D questionnaire is for number of participants who achieved CR or CRi at month 60. The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain & discomfort, anxiety & depression. Respondents are asked to choose the statement in each dimension that best describes their health status on the day surveyed. Their responses are coded as a number (1, 2, or 3) that corresponds to the respective level of severity: 1 indicates no problems, 2 some problems, and 3 severe problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state. The scores are then normalized to a value from 0-100 where higher scores = better HRQOL & fewer problems or symptoms.

End point type	Secondary

End point timeframe:

Month 60

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Participants				
M60: Mobility - No problems	15			
M60: Mobility - Some problems	1			
M60: Mobility - Severe problems	0			
M60: Self-care - No problems	16			

M60: Self-care - Some problems	0			
M60: Self-care - Severe problems	0			
M60: Usual activities - No problems	15			
M60: Usual activities - Some problems	0			
M60: Usual activities - Severe problems	1			
M60: Pain/discomfort - No problems	14			
M60: Pain/discomfort - Some problems (n =	2			
M60: Pain/discomfort - Severe problems	0			
M60: Anxiety/depression - No problems	12			
M60: Anxiety/depression - Some problems	4			
M60: Anxiety/depression - Severe problems	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Develop a score utilizing clinical and biomarker data and assess its ability for early prediction of cytokine release syndrome

End point title	Develop a score utilizing clinical and biomarker data and assess its ability for early prediction of cytokine release syndrome

End point description:

Derivation of a score to predict cytokine release syndrome.
Considering the complexity and challenges of building a scoring system based on limited data from the trial, this analysis was not performed.

End point type	Secondary

End point timeframe:

3 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: scores on a scale				
median (full range (min-max))	(to)			

Notes:

[2] - Building a scoring system based on limited data was too complex, so analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Frequent monitoring of concentrations of soluble immune factors in blood (C Reactive Protein & Ferritin)

End point title	Frequent monitoring of concentrations of soluble immune factors in blood (C Reactive Protein & Ferritin)

End point description:	
Profile of soluble immune factors of key inflammatory markers and cytokine parameters in blood by maximum CRS grade that may be key to cytokine release syndrome (CRS).	
End point type	Secondary
End point timeframe:	
Maximum post-baseline (approx. 60 months)	

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: mg/L				
geometric mean (geometric coefficient of variation)				
C Reactive Protein:Fold-change from BL Grade 4 CRS	9.33 (± 303.9)			
Ferritin: Fold-change from BL Grade 4 CRS	36.62 (± 164.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Frequent monitoring of concentrations of soluble immune factors in blood (all other inflammatory markers)

End point title	Frequent monitoring of concentrations of soluble immune factors in blood (all other inflammatory markers)
End point description:	
Profile of soluble immune factors of key inflammatory markers and cytokine parameters in blood by maximum CRS grade that may be key to cytokine release syndrome (CRS).	
End point type	Secondary
End point timeframe:	
Maximum post-baseline (approx. 60 months)	

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
Interferon gamma:Fold-change from BL Gr 4 CRS	2745.92 (± 1186.3)			
Interleukin 10: Fold-change from BL Grade 4 CRS	179.49 (± 966.7)			
Interleukin 12p70: Fold-change from BL Grade 4 CRS	93.50 (± 261.0)			

Interleukin 13: Fold-change from BL Grade 4 CRS	49.21 (± 124.0)			
Interleukin 1 beta: Fold-change from BL Gr. 4 CRS	16.75 (± 127.7)			
Interleukin 2: Fold-change from BL Gr. 4 CRS	337.86 (± 161.1)			
Interleukin 4: Fold-change from BL Grade 4 CRS	170.21 (± 163.3)			
Interleukin 6: Fold-change from BL Grade 4 CRS	1435.85 (± 221.6)			
Interleukin 8: Fold-change from BL Grade 4 CRS	139.40 (± 246.9)			
Tum necrosis factr alpha:Fold-chg from BL Gr 4 CRS	27.13 (± 223.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of levels of B and T Cells (Blood and Bone Marrow) prior to and following CTL019 Infusion

End point title	Change from baseline of levels of B and T Cells (Blood and Bone Marrow) prior to and following CTL019 Infusion

End point description:

Levels of B and T cells (blood and bone marrow) prior to and following CTL019 infusion for safety monitoring

End point type	Secondary

End point timeframe:

Month 3, Month 12, Maximum post-baseline (approx. 60 months)

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
M3: change from BL - (B cell) CR/CRi	-25.37 (± 31.693)			
M3: change from BL - (B cell) NR	-37.93 (± 35.882)			
M3: change from BL - (B cell) Unknown	-11.01 (± 6.649)			
M3: change from BL - (B cell) All participants	-24.23 (± 30.215)			
M12: change from BL - (B cell) CR/CRi	-18.55 (± 27.144)			
M12: change from BL - (B cell) NR	-55.21 (± 999)			
M12: change from BL - (B cell) Unknown	-12.04 (± 5.995)			
M12 change from BL -: (B cell) All Participants	-19.00 (± 26.432)			

Maximum post-BL: (B cell) CR/CRi	-21.25 (± 37.618)			
Maximum post-BL: (B cell) NR	2.10 (± 66.398)			
Maximum post-BL: (B cell) Unknown	7.98 (± 29.536)			
Maximum post-BL: (B cell) All participants	-15.60 (± 40.336)			
M3: change from BL - (T cell) All participants	-11.91 (± 32.333)			
M12: change from BL - (T cell) All participants	-1.68 (± 36.228)			
Maximum post-BL: (T cell) All participants	34.12 (± 29.450)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Overall remission rate (ORR) - from Fraunhofer Institute manufacturing facility

End point title	Percentage of participants with Overall remission rate (ORR) - from Fraunhofer Institute manufacturing facility

End point description:

These are the percentage of participants with ORR who achieved overall remission rate which includes complete response (CR) and CR with incomplete blood count recovery (CRi) as determined by IRC assessment after having been infused with tisagenlecleucel from Fraunhofer Institute manufacturing facility.

End point type	Secondary

End point timeframe:

60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Percentage of participants				
number (confidence interval 95%)	83.3 (51.6 to 97.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Best Overall Response (BOR) of CR or CRi with minimal residue disease (MRD) negative bone marrow from Fraunhofer Institute manufacturing facility as per IRC

End point title	Percentage of participants with Best Overall Response (BOR) of CR or CRi with minimal residue disease (MRD) negative bone

	marrow from Fraunhofer Institute manufacturing facility as per IRC

End point description:

These are the percentage of participants who achieved Best Overall Response (BOR) of CR or CRi with an MRD-negative bone marrow by central analysis using flow cytometry among participants who received tisagenlecleucel from Fraunhofer Institute manufacturing facilities only, by IRC assessment.

End point type	Secondary

End point timeframe:

3 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Percentage of participants				
number (confidence interval 95%)	75.0 (42.8 to 94.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tisagenlecleucel transgene levels by qPCR in blood, bone marrow and CSF if available - tisagenlecleucel manufactured from Fraunhofer Institute

End point title	Tisagenlecleucel transgene levels by qPCR in blood, bone marrow and CSF if available - tisagenlecleucel manufactured from Fraunhofer Institute

End point description:

This is the summary of cellular kinetic concentrations for Tisagenlecleucel (CTL019) transgene levels by qPCR, by day 28 disease response by IRC assessment. The assessment of the efficacy, safety and in vivo cellular pharmacokinetics are for patients infused with tisagenlecleucel manufactured by Fraunhofer Institute.

End point type	Secondary

End point timeframe:

Month 60 (peripheral blood), Month 3 (bone marrow)

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: copies/ug				
geometric mean (geometric coefficient of variation)				
M60: (Cmax) PB CTL019 Transgene: All participants M3: BM CTL019 Transgene: All Participants (n = 7)	42800 (± 117.7) 855 (± 792.6)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths

End point description:

On-treatment deaths, which include post-treatment survival follow-up deaths, were collected during the post-infusion period (starting at the day of first infusion until the end of the study, approx. 60 months All deaths refers to the sum of on-treatment deaths and post-treatment survival follow-up deaths up to approx. 60 months.

End point type	Post-hoc

End point timeframe:

On-treatment deaths: Up to 60 months; Post-treatment survival follow-up deaths: Up to approx. 60 months

End point values	Single dose of CTL019			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Participants				
On-treatment deaths incl post-trt surv. f/u deaths	33			
All deaths	33			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs - collected during post-infusion period up to max. duration of 60 months for each patient. Deaths - collected at all points post-trt (incl. post-trt survival f/u period) until patient completed 60 months or further safety f/u under study protocol.

Adverse event reporting additional description:

AE: Any sign or symptom that occurs during post-infusion period (starting at day of first infusion of CTL019 until end of the study) & safety follow-up. Deaths in post treatment survival follow-up are not considered AEs. The total number at risk in post treatment survival includes patients who entered post treatment survival follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	All@patients

Reporting group description:

All@patients

Serious adverse events	All@patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 80 (78.75%)		
number of deaths (all causes)	33		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone giant cell tumour benign			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences causally related to treatment / all	8 / 9		
deaths causally related to treatment / all	0 / 0		

Venoocclusive disease				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General disorders and administration site conditions				
Non-cardiac chest pain				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	7 / 80 (8.75%)			
occurrences causally related to treatment / all	3 / 11			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	3 / 80 (3.75%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 1			
Immune system disorders				
Drug hypersensitivity				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytokine release syndrome				
subjects affected / exposed	50 / 80 (62.50%)			
occurrences causally related to treatment / all	51 / 51			
deaths causally related to treatment / all	0 / 0			
Allergy to immunoglobulin therapy				

subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemophagocytic lymphohistiocytosis				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Reproductive system and breast disorders				
Endometriosis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchial oedema				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				

subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Laryngeal oedema				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	5 / 80 (6.25%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	5 / 80 (6.25%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Delirium				

subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood bilirubin increased				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood uric acid increased				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Infusion related reaction				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vasoplegia syndrome				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	3 / 80 (3.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Cardiac failure			
subjects affected / exposed	2 / 80 (2.50%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block first degree			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Dysarthria			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Encephalopathy				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Disseminated intravascular coagulation				
subjects affected / exposed	3 / 80 (3.75%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	15 / 80 (18.75%)			
occurrences causally related to treatment / all	14 / 18			
deaths causally related to treatment / all	0 / 0			
Coagulopathy				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Thrombocytopenia				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal compartment syndrome				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Irritable bowel syndrome				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic colitis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				

subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatomegaly				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal tubular necrosis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	5 / 80 (6.25%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Rhabdomyolysis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Haemarthrosis			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	3 / 80 (3.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
COVID-19			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection			

reactivation				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Candida infection				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Encephalitis				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Gastroenteritis salmonella				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis Escherichia coli				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enterobacter infection				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalitis viral				

subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Meningitis bacterial				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella infection				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Human herpesvirus 6 infection				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis pneumococcal				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metapneumovirus infection				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ophthalmic herpes zoster				

subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis externa				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia fungal				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia respiratory syncytial viral				

subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 80 (3.75%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal abscess				

subjects affected / exposed	1 / 80 (1.25%)			
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 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	3 / 80 (3.75%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Viral haemorrhagic cystitis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella zoster virus infection				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypercalcaemia				

subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypernatraemia				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperphosphataemia				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour lysis syndrome				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolic acidosis				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Malnutrition				

subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All@patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 80 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	18 / 80 (22.50%)		
occurrences (all)	18		
Hypertension			
subjects affected / exposed	16 / 80 (20.00%)		
occurrences (all)	17		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	31 / 80 (38.75%)		
occurrences (all)	42		
Generalised oedema			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Fatigue			

subjects affected / exposed	17 / 80 (21.25%)		
occurrences (all)	19		
Face oedema			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	9		
Chills			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	8		
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	33 / 80 (41.25%)		
occurrences (all)	40		
Cytokine release syndrome			
subjects affected / exposed	37 / 80 (46.25%)		
occurrences (all)	37		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	7		
Dyspnoea			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	7		
Cough			
subjects affected / exposed	23 / 80 (28.75%)		
occurrences (all)	29		
Tachypnoea			
subjects affected / exposed	9 / 80 (11.25%)		
occurrences (all)	11		
Rhinorrhoea			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	8		
Pulmonary oedema			
subjects affected / exposed	11 / 80 (13.75%)		
occurrences (all)	11		
Oropharyngeal pain			

subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	9		
Nasal congestion			
subjects affected / exposed	9 / 80 (11.25%)		
occurrences (all)	10		
Hypoxia			
subjects affected / exposed	16 / 80 (20.00%)		
occurrences (all)	19		
Pleural effusion			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	8		
Psychiatric disorders			
Delirium			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	7		
Confusional state			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	7		
Anxiety			
subjects affected / exposed	14 / 80 (17.50%)		
occurrences (all)	14		
Agitation			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	7		
Investigations			
C-reactive protein increased			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	7		
Alanine aminotransferase increased			
subjects affected / exposed	18 / 80 (22.50%)		
occurrences (all)	21		
Aspartate aminotransferase increased			

subjects affected / exposed	18 / 80 (22.50%)			
occurrences (all)	19			
Blood bilirubin increased				
subjects affected / exposed	12 / 80 (15.00%)			
occurrences (all)	20			
Blood creatinine increased				
subjects affected / exposed	5 / 80 (6.25%)			
occurrences (all)	5			
Blood fibrinogen decreased				
subjects affected / exposed	7 / 80 (8.75%)			
occurrences (all)	7			
Blood lactate dehydrogenase increased				
subjects affected / exposed	5 / 80 (6.25%)			
occurrences (all)	5			
Blood immunoglobulin M decreased				
subjects affected / exposed	7 / 80 (8.75%)			
occurrences (all)	7			
Blood immunoglobulin A decreased				
subjects affected / exposed	7 / 80 (8.75%)			
occurrences (all)	7			
Electrocardiogram QT prolonged				
subjects affected / exposed	5 / 80 (6.25%)			
occurrences (all)	5			
International normalised ratio increased				
subjects affected / exposed	9 / 80 (11.25%)			
occurrences (all)	10			
Lymphocyte count decreased				
subjects affected / exposed	17 / 80 (21.25%)			
occurrences (all)	23			
Neutrophil count decreased				
subjects affected / exposed	24 / 80 (30.00%)			
occurrences (all)	42			
Platelet count decreased				

subjects affected / exposed	24 / 80 (30.00%)		
occurrences (all)	35		
Serum ferritin increased			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	8		
White blood cell count decreased			
subjects affected / exposed	25 / 80 (31.25%)		
occurrences (all)	43		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	17 / 80 (21.25%)		
occurrences (all)	22		
Nervous system disorders			
Tremor			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	7		
Somnolence			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	27 / 80 (33.75%)		
occurrences (all)	37		
Encephalopathy			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	13 / 80 (16.25%)		
occurrences (all)	15		
Disseminated intravascular coagulation			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Anaemia			
subjects affected / exposed	25 / 80 (31.25%)		
occurrences (all)	38		
Thrombocytopenia			

subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	10		
Neutropenia			
subjects affected / exposed	11 / 80 (13.75%)		
occurrences (all)	15		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	13 / 80 (16.25%)		
occurrences (all)	15		
Abdominal pain			
subjects affected / exposed	11 / 80 (13.75%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	25 / 80 (31.25%)		
occurrences (all)	35		
Nausea			
subjects affected / exposed	21 / 80 (26.25%)		
occurrences (all)	26		
Mouth haemorrhage			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	24 / 80 (30.00%)		
occurrences (all)	27		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	6		
Hyperbilirubinaemia			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	9		
Erythema			

subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Dry skin			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	8		
Rash			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	11		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 80 (11.25%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 80 (15.00%)		
occurrences (all)	14		
Back pain			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	11		
Myalgia			
subjects affected / exposed	10 / 80 (12.50%)		
occurrences (all)	11		
Pain in extremity			
subjects affected / exposed	17 / 80 (21.25%)		
occurrences (all)	18		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	12		
Rhinovirus infection			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	8		
Sinusitis			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	13		
Staphylococcal infection			

subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	12 / 80 (15.00%)		
occurrences (all)	13		
Nasopharyngitis			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 80 (37.50%)		
occurrences (all)	30		
Hyperglycaemia			
subjects affected / exposed	9 / 80 (11.25%)		
occurrences (all)	10		
Hyperuricaemia			
subjects affected / exposed	9 / 80 (11.25%)		
occurrences (all)	12		
Hypervolaemia			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	7		
Hypoalbuminaemia			
subjects affected / exposed	11 / 80 (13.75%)		
occurrences (all)	14		
Hypocalcaemia			
subjects affected / exposed	16 / 80 (20.00%)		
occurrences (all)	19		
Hypokalaemia			
subjects affected / exposed	20 / 80 (25.00%)		
occurrences (all)	25		
Hypomagnesaemia			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	7		
Hypophosphataemia			
subjects affected / exposed	18 / 80 (22.50%)		
occurrences (all)	22		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2015	The window between informed consent and tisagenlecleucel infusion was widened from 8 weeks to 16 weeks. - Included additional safety information to address FDA requirements for CRS, deaths, follow-up after live birth. - Updated secondary endpoints to include expression of tisagenlecleucel in blood and bone marrow by flow cytometry and some exploratory endpoints - Updated study design diagram with extended windows from ICF to infusion. - Updated vital signs follow-up post tisagenlecleucel infusion. - Changed age at Screening from 2 years at initial diagnosis to 3 years at Screening. - Added an additional inclusion criteria to confirm patient met local institutional criteria for leukapheresis. - Added resource utilization to capture hospitalizations. Added PROs.
22 May 2015	- Modified to include that the FAS should contain at least 50 patients < 18 years (of which 10 patients should be < 10-years-old). The total number of planned patient enrolment was increased accordingly to approximately 78. - Upgraded MRD by PCR from secondary to key secondary endpoint, based on its relevance as a surrogate marker correlated with clinical benefit in p-ALL. - Upgraded CRS, safety monitoring, and PROs endpoints from exploratory to secondary endpoints. - Added derivation of a score to predict CRS as a secondary objective. - Changed Day 28 tumor assessment window from ±7 days to ±4 days. - Additional analyses had been included to assess the response at Day 28±4 days, impact of Baseline tumor burden on response, etc. - Extended healthcare resource utilization collection visits. - Removed PedsQL questionnaire collection in children ages 5 to 7 years.
13 April 2016	- Expanded target tisagenlecleucel dose range for patients > 50 kg and defined allowable dose ranges. - Extended the allowance of more than 10 patients ≥ 18 years old. - Updated the CRS algorithm and management guidelines (including the use of siltuximab). - Updated pediatric ALL efficacy guidelines. - Updated the AESI list to include: febrile neutropenia, infections, transient neuropsychiatric events, and hematopoietic cytopenias lasting ≥ 28 days.
14 June 2016	- Updated the definition of the primary efficacy endpoint. Based on published data with tisagenlecleucel, clinical trial experience thus far, and based upon discussions with FDA, the post infusion follow-up duration for assessing the primary objective of ORR for each patient was changed from 6 months to 3 months. - Added the EU manufacturing facility as an additional manufacturing facility and increase the enrolment target to allow up to 14 patients treated with tisagenlecleucel from this facility. - Defined two new key efficacy endpoints to allow evaluation of ORR and MRD-negative ORR only for tisagenlecleucel manufactured at the US facility.
04 April 2017	- Enrolled 5 additional Japanese patients in the study to include at least 3 additional patients infused with tisagenlecleucel manufactured from the US facility. - Provided a modified CRS management algorithm for Japanese patients as anti-IL6 drugs other than tocilizumab are not available in Japan.

21 March 2019	- Additional 20 patients to be screened in the two cohorts and at least 15 of them to be treated with tisagenlecleucel - (1) pediatric ALL patients who are very high risk at the time of first relapse; (2) relapse within 6 months of an allogeneic HSCT. This recruitment was limited to the US sites. - Changed CRS grading scale to Lee et al 2014 and updated the CRS management algorithm.
26 October 2020	- Terminate the enrollment into Cohorts 1 and 2 as patient enrollment was low subsequently, due to availability of alternative treatment options. One patient was treated in Cohort 1 and no patient was enrolled or treated in Cohort 2. A notification was sent to FDA on 26-Jun-2020 to communicate the decision to terminate patient enrollment to these two cohorts. - Change the follow-up requirement to determine the outcome of a pregnancy. This additional safety monitoring was not due to any new safety concern, but a precautionary measure. - Add the requirement for pregnancy testing at all study visits. - Clarify the requirements for laboratory testing (to include RCL testing) in the case of secondary malignancies and specify that blood samples for RCL testing were to be stored beyond Month 12, as long as all samples through Month 12 were negative.

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: