Clinical trial results:
A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR zeta and 4-1BB Signaling Domains in Subjects with Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma.

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

Summary

EudraCT number	2017-002849-30
Trial protocol	Outside EU/EEA
Global end of trial date	07 May 2018

Results information

Result version number	v1 (current)
This version publication date	01 July 2020
First version publication date	01 July 2020

Trial information

Trial identification

Sponsor protocol code	CTL019B2101J

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01626495
WHO universal trial number (UTN)	-
Other trial identifiers	CHP-959: CHP-959

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	Yes

investigation plan (PIP)	
EMA paediatric investigation plan number(s)	EMEA-001654-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
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	07 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were:
- to determine the safety and feasibility of administration of chimeric antigen receptor T cells transduced with the anti-CD19 lentiviral vector (referred to as tisagenlecleucel), in subjects who either had not received a prior allogeneic stem cell transplantation (SCT) or had 0% residual donor engraftment (“no allo” cohort), or had relapsed after prior allogeneic SCT with any degree of residual donor engraftment (“allo” cohort)

- to determine the duration of in vivo survival of tisagenlecleucel cells. Real-time polymerase chain reaction analysis of whole blood was used to detect and quantify survival of tisagenlecleucel TCRζ:4-1BB and TCRζ cells over time.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2012
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: 62
Worldwide total number of subjects	62
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)	1
Children (2-11 years)	30
Adolescents (12-17 years)	23
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

73 subjects were enrolled in this study, and 62 subjects (57 non-CNS3 ALL subjects, 4 CNS3 ALL subjects, and 1 lymphoma subjects) received one or more tisagenlecleucel infusions.

Pre-assignment

Screening details:

Subjects will be identified through the clinical practices of the investigator or sub-investigators and through referrals from outside hospitals and physicians. No direct -to-patient advertising will be performed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CTL019 (Non-CNS3)

Arm description:

This was a single arm open-label study where each subject was infused with CTL019.

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

Dosage and administration details:

A total dose of ~1.5×107 to 5×109 (~0.3x106 to 1.0×108/kg) T cells was infused.

Arm title	CTL019 (CNS3)

Arm description:

This was a single arm open-label study where each subject was infused with CTL019.

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

Dosage and administration details:

A total dose of ~1.5×107 to 5×109 (~0.3x106 to 1.0×108/kg) T cells was infused.

Arm title	CTL019 (lymphoma)

Arm description:

This was a single arm open-label study where each subject was infused with CTL019.

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

Dosage and administration details:
A total dose of ~1.5×107 to 5×109 (~0.3x106 to 1.0×108/kg) T cells was infused.

Number of subjects in period 1	CTL019 (Non-CNS3)	CTL019 (CNS3)	CTL019 (lymphoma)
Started	57	4	1
Completed	20	1	0
Not completed	37	3	1
Adverse event, serious fatal	-	1	-
New cancer therapy	16	-	-
Disease Progression	21	2	1

Baseline characteristics

Reporting groups	
Reporting group title	CTL019 (Non-CNS3)
Reporting group description:	
This was a single arm open-label study where each subject was infused with CTL019.	
Reporting group title	CTL019 (CNS3)
Reporting group description:	
This was a single arm open-label study where each subject was infused with CTL019.	
Reporting group title	CTL019 (lymphoma)
Reporting group description:	
This was a single arm open-label study where each subject was infused with CTL019.	

Reporting group values	CTL019 (Non-CNS3)	CTL019 (CNS3)	CTL019 (lymphoma)
Number of subjects	57	4	1
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	1	0	0
Children (2-11 years)	30	0	0
Adolescents (12-17 years)	20	2	1
Adults (18-64 years)	6	2	0
Age continuous Units: years			
arithmetic mean	11.6	19.5	12.0
standard deviation	± 5.06	± 5.97	± 0.0
Gender categorical Units: Subjects			
Female	25	2	1
Male	32	2	0

Reporting group values	Total		
Number of subjects	62		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	1		
Children (2-11 years)	30		
Adolescents (12-17 years)	23		
Adults (18-64 years)	8		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	28		
Male	34		

End points

End points reporting groups

Reporting group title	CTL019 (Non-CNS3)
Reporting group description:	
This was a single arm open-label study where each subject was infused with CTL019.	
Reporting group title	CTL019 (CNS3)
Reporting group description:	
This was a single arm open-label study where each subject was infused with CTL019.	
Reporting group title	CTL019 (lymphoma)
Reporting group description:	
This was a single arm open-label study where each subject was infused with CTL019.	
Subject analysis set title	CR/CRi
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with Complete remission (CR) and/or Complete remission with incomplete blood count recovery (CRi).	
Subject analysis set title	NR
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with No remission (NR)	

Primary: Occurrence of study related adverse events (Non-CNS3)

End point title	Occurrence of study related adverse events (Non-CNS3)[1][2]
End point description:	
This is defined as NCI CTC > grade 3 signs/symptoms, laboratory toxicities and clinical events that are possible, likely or definitely related to study treatment at any time from the infusion until week 24.	
End point type	Primary
End point timeframe:	
from the infusion until week 24	

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

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

End point values	CTL019 (Non-CNS3)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: subjects				
Subjects with at least one Adverse Event (AE)	57			
Subjs - at least 1 AE susp. to be study drug rel.	57			
Subjs with AE grade 3/4 susp.to be study drug rel.	55			
Deaths:any prim. system organ class(SOC):Study ind	27			
Deaths:within 30 days of last inf: any primary SOC	3			

Deaths: within 30 days of last inf.: study indic.	3			

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral blood PK parameters for CTL019 transgene levels by qPCR, by day 28 disease response for Non-CNS3 ALL subjects: AUC

End point title	Peripheral blood PK parameters for CTL019 transgene levels by qPCR, by day 28 disease response for Non-CNS3 ALL subjects: AUC[3]

End point description:

Duration of in vivo survival of CTL019 cells is defined as "engraftment". This is the # DNA vector copies per ml blood of CTL019 cells on week 4 after the first infusion. Q-PCR for CTL019 vector sequences were performed after each infusion, weekly x 4, monthly x 6, and every 3 months thereafter until any 2 sequential tests were negative documenting loss of CTL019 cells.

End point type	Primary

End point timeframe:

from the infusion until week 24

Notes:

[3] - 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	CR/CRi	NR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	3		
Units: copies/ug*days				
geometric mean (geometric coefficient of variation)				
AUC 0-28d (n = 53, 2)	305000 (± 200.8)	236000 (± 1910.7)		
AUC 0-84d (n = 42, 0)	467000 (± 139.6)	0.0 (± 0.0)		
AUC Tmax-28d (n = 49, 2)	174000 (± 203.2)	12000 (± 4138.0)		
AUC Tmax-84d (n= 42, 0)	323000 (± 146.0)	0.0 (± 0.0)		
AUC 0-Tmax (n = 53, 3)	110000 (± 209.6)	43700 (± 1090.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral blood PK parameters for CTL019 transgene levels by qPCR, by day 28 disease response for Non-CNS3 ALL subjects: Cmax, Clast

End point title	Peripheral blood PK parameters for CTL019 transgene levels by qPCR, by day 28 disease response for Non-CNS3 ALL subjects: Cmax, Clast[4]

End point description:

Duration of in vivo survival of CTL019 cells is defined as "engraftment". This is the # DNA vector copies per ml blood of CTL019 cells on week 4 after the first infusion. Q-PCR for CTL019 vector sequences were performed after each infusion, weekly x 4, monthly x 6, and every 3 months thereafter until any 2 sequential tests were negative documenting loss of CTL019 cells.

End point type	Primary

End point timeframe:

from the infusion until week 24

Notes:

[4] - 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	CR/CRi	NR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	3		
Units: copies/ug				
geometric mean (geometric coefficient of variation)				
Cmax (n = 54, 3)	40700 (± 176.4)	17200 (± 779.4)		
Clast (n = 38, 0)	180 (± 433.9)	0.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral blood PK parameters for CTL019 transgene levels by qPCR, by day 28 disease response for Non-CNS3 ALL subjects: Tmax, Tlast

End point title	Peripheral blood PK parameters for CTL019 transgene levels by qPCR, by day 28 disease response for Non-CNS3 ALL subjects: Tmax, Tlast[5]

End point description:

Duration of in vivo survival of CTL019 cells is defined as "engraftment". This is the # DNA vector copies per ml blood of CTL019 cells on week 4 after the first infusion. Q-PCR for CTL019 vector sequences were performed after each infusion, weekly x 4, monthly x 6, and every 3 months thereafter until any 2 sequential tests were negative documenting loss of CTL019 cells.

End point type	Primary

End point timeframe:

from the infusion until week 24

Notes:

[5] - 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	CR/CRi	NR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	3		
Units: days				
median (full range (min-max))				
Tmax (54, 3)	11.0 (2.00 to 31.0)	13.0 (8.0 to 16.0)		
Tlast (n = 38, 0)	180 (18.0 to 784)	0.0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral blood PK parameters for CTL019 transgene levels by qPCR, by day 28 disease response for Non-CNS3 ALL subjects: T1/2

End point title	Peripheral blood PK parameters for CTL019 transgene levels by qPCR, by day 28 disease response for Non-CNS3 ALL subjects: T1/2[6]

End point description:

Duration of in vivo survival of CTL019 cells is defined as "engraftment". This is the # DNA vector copies per ml blood of CTL019 cells on week 4 after the first infusion. Q-PCR for CTL019 vector sequences were performed after each infusion, weekly x 4, monthly x 6, and every 3 months thereafter until any 2 sequential tests were negative documenting loss of CTL019 cells.

End point type	Primary

End point timeframe:

from the infusion until week 24

Notes:

[6] - 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	CR/CRi	NR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	2		
Units: days				
geometric mean (geometric coefficient of variation)				
T1/2 (n = 38, 2)	21.6 (± 387.3)	4.66 (± 206.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral blood PK parameters for analyte % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL subjects: AUC

End point title	Peripheral blood PK parameters for analyte % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL

	subjects: AUC[7]
End point description:	
CAR+ cells measured by flow cytometry	
End point type	Primary
End point timeframe:	
from the infusion until week 24	

Notes:

[7] - 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	CR/CRi	NR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	3		
Units: %*days				
geometric mean (geometric coefficient of variation)				
AUC 0-28d (n= 52, 2)	242 (± 128.5)	15.5 (± 496.2)		
AUC 0-84d (n= 42 0)	366 (± 130.5)	0.0 (± 0.0)		
AUC Tmax-28 (n= 49, 2)	139 (± 147.6)	5.03 (± 134.9)		
AUC Tmax-84d (n=42, 0)	237 (± 153.9)	0.0 (± 0.0)		
AUC 0-Tmax (n = 20, 2)	66.0 (± 150.8)	9.27 (± 1227.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral blood PK parameters for % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL subjects: Cmax, Clast

End point title	Peripheral blood PK parameters for % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL subjects: Cmax, Clast[8]
End point description:	
CAR+ cells measured by flow cytometry	
End point type	Primary
End point timeframe:	
from infusion until 24 months	

Notes:

[8] - 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	CR/CRi	NR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	3		
Units: Percentage				
geometric mean (geometric coefficient of variation)				

Cmax (n =54, 3) Clast (n = 50, 3)	30.3 (± 100.5) 0.240 (± 190.5)	0.990 (± 608.8) 0.130 (± 41.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral blood PK parameters for % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL subjects: Tmax, Tlast

End point title	Peripheral blood PK parameters for % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL subjects: Tmax, Tlast[9]

End point description:

CAR+ cells measured by flow cytometry

End point type	Primary

End point timeframe:

from infusion until week 24

Notes:

[9] - 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	CR/CRi	NR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	3		
Units: days				
median (full range (min-max))				
Tmax (n = 54, 3) Tlast (n = 43, 2)	11.0 (7.00 to 31.0) 119 (18.0 to 780)	13.0 (8.00 to 13.0) 21.0 (13.0 to 29.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral blood PK parameters for % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL subjects: T1/2

End point title	Peripheral blood PK parameters for % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL subjects: T1/2[10]

End point description:

CAR+ cells measured by flow cytometry

End point type	Primary

End point timeframe:

from infusion until week 24

Notes:

[10] - 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	CR/CRi	NR		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	1		
Units: days				
geometric mean (geometric coefficient of variation)				
T1/2 (n= 50, 1)	11.8 (± 159.2)	7.36 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) for Non-CNS3 ALL subjects

End point title	Overall Response Rate (ORR) for Non-CNS3 ALL subjects[11]

End point description:

ORR, defined as the percentage of patients with a best overall disease response of CR or CRi, was assessed in the full analysis set (FAS).
The CR rate at Day 28 was defined as the proportion of patients with an overall disease response of CR or CRi at Day 28 visit. Disease assessment performed between study Day 2 to Day 59 and prior to new therapy were considered within the window.
Flow-based clinical minimal residual disease (MRD) assessment was performed and is the percentage of patients
achieving MRD negative bone marrow post-infusion and before relapse, among all patients who achieved CR or CRi.

End point type	Secondary

End point timeframe:

from the infusion until week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

End point values	CTL019 (Non-CNS3)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percentage of subjects				
number (confidence interval 95%)				
ORR (CR + CRi) at day 28	94.7 (85.4 to 98.9)			
ORR with bone marrow with MRD negative at Day 28	86.0 (74.2 to 93.7)			
ORR	94.7 (85.4 to 98.9)			
ORR with bone marrow MRD negative	89.5 (78.5 to 96.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) for non-CNS3 ALL subjects

End point title	Duration of response (DoR) for non-CNS3 ALL subjects[12]

End point description:

DOR was defined as the duration from the date when the response criteria of CR or CRi was first met to the date of relapse or death due to underlying cancer. DOR was assessed only in patients with the BOR of CR or CRi.

End point type	Secondary

End point timeframe:

from the infusion until week 24

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

End point values	CTL019 (Non-CNS3)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: months				
median (confidence interval 95%)	27.9 (8.0 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free survival (RFS) for non-CNS3 ALL subjects

End point title	Relapse-free survival (RFS) for non-CNS3 ALL subjects[13]

End point description:

RFS was measured by the time from the achievement of CR or CRi whatever occurred first to relapse or death due to any cause during CR or CRi. RFS was assessed only in patients with the BOR of CR or CRi.

End point type	Secondary

End point timeframe:

from the infusion until week 24

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

End point values	CTL019 (Non-CNS3)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: months				
median (confidence interval 95%)	27.9 (8.0 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event free survival (EFS) for non-CNS3 ALL subjects

End point title	Event free survival (EFS) for non-CNS3 ALL subjects[14]

End point description:

EFS was defined as the time from date of first CTL019 infusion to the earliest of the following: Death from any cause, Relapse, Treatment failure: defined as NR in the study and discontinuation from the study due to any of the following reasons: AE (including abnormal laboratory values or abnormal test procedure results), Progressive disease, New anticancer therapy

End point type	Secondary

End point timeframe:

from the infusion until week 24

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

End point values	CTL019 (Non-CNS3)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: months				
median (confidence interval 95%)	24.9 (8.6 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) for non-CNS3 ALL subjects

End point title	Overall survival (OS) for non-CNS3 ALL subjects[15]

End point description:

OS was the time from the date of first CTL019 infusion to the date of death due to any reason.

End point type	Secondary

End point timeframe:

from the infusion until week 24

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

End point values	CTL019 (Non-CNS3)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: months				
median (confidence interval 95%)	47.7 (28.3 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response (BOR) for non-CNS3 ALL subjects

End point title	Best overall response (BOR) for non-CNS3 ALL subjects[16]

End point description:

BOR is the best response over all the response assessments according to the sequence from best to the worst: CR-Cri-No response.

End point type	Secondary

End point timeframe:

from infusion until 24 weeks

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

End point values	CTL019 (Non-CNS3)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percentage of subjects				
number (not applicable)				
CR	73.7			
CRi	21.1			
No response	5.3			

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	All patients

Reporting group description:

All subjects who received one or more tisagenlecleucel infusions

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 62 (91.94%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	0		
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences causally related to treatment / all	11 / 11		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	24 / 62 (38.71%)		
occurrences causally related to treatment / all	24 / 25		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Complication associated with device			

subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial pain				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	15 / 62 (24.19%)			
occurrences causally related to treatment / all	20 / 26			
deaths causally related to treatment / all	0 / 0			
Vascular stent thrombosis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytokine release syndrome				
subjects affected / exposed	52 / 62 (83.87%)			
occurrences causally related to treatment / all	62 / 62			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	4 / 62 (6.45%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			

Acute respiratory failure				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Apnoea				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	10 / 62 (16.13%)			
occurrences causally related to treatment / all	9 / 10			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory alkalosis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				

subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Weight decreased				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Lower limb fracture				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transfusion reaction				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Central nervous system haemorrhage			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Encephalopathy			
subjects affected / exposed	17 / 62 (27.42%)		
occurrences causally related to treatment / all	18 / 18		
deaths causally related to treatment / all	0 / 0		
Facial paresis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Headache				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	4 / 62 (6.45%)			
occurrences causally related to treatment / all	5 / 7			
deaths causally related to treatment / all	0 / 0			
Speech disorder				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Unresponsive to stimuli				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Coagulopathy				
subjects affected / exposed	3 / 62 (4.84%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	6 / 62 (9.68%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	46 / 62 (74.19%)			
occurrences causally related to treatment / all	57 / 60			
deaths causally related to treatment / all	0 / 0			
Haemolysis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Hypofibrinogenaemia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
BK virus infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Enterococcal bacteraemia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastroenteritis salmonella			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyomyositis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Staphylococcal infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal skin infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stenotrophomonas infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatococcal infection			

subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal infection				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella zoster virus infection				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	5 / 62 (8.06%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour lysis syndrome				

subjects affected / exposed	1 / 62 (1.61%)		
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	62 / 62 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	14		
Hypotension			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	16		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	27 / 62 (43.55%)		
occurrences (all)	32		
Fatigue			
subjects affected / exposed	29 / 62 (46.77%)		
occurrences (all)	48		
Pain			
subjects affected / exposed	28 / 62 (45.16%)		
occurrences (all)	34		
Pyrexia			
subjects affected / exposed	15 / 62 (24.19%)		
occurrences (all)	19		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	6		
Hypogammaglobulinaemia			
subjects affected / exposed	42 / 62 (67.74%)		
occurrences (all)	78		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 62 (56.45%)		
occurrences (all)	53		
Dyspnoea			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	15 / 62 (24.19%)		
occurrences (all)	23		
Hypoxia			
subjects affected / exposed	9 / 62 (14.52%)		
occurrences (all)	10		
Nasal congestion			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	14		
Oropharyngeal pain			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Pleural effusion			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Rhinorrhoea			
subjects affected / exposed	16 / 62 (25.81%)		
occurrences (all)	24		
Tachypnoea			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	11		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	7		
Confusional state			
subjects affected / exposed	15 / 62 (24.19%)		
occurrences (all)	15		
Insomnia			

subjects affected / exposed	8 / 62 (12.90%)		
occurrences (all)	8		
Product issues			
Device occlusion			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	5		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	22 / 62 (35.48%)		
occurrences (all)	33		
Alanine aminotransferase increased			
subjects affected / exposed	45 / 62 (72.58%)		
occurrences (all)	78		
Aspartate aminotransferase increased			
subjects affected / exposed	46 / 62 (74.19%)		
occurrences (all)	111		
Blood bilirubin increased			
subjects affected / exposed	15 / 62 (24.19%)		
occurrences (all)	18		
Blood creatinine increased			
subjects affected / exposed	23 / 62 (37.10%)		
occurrences (all)	53		
Blood fibrinogen decreased			
subjects affected / exposed	11 / 62 (17.74%)		
occurrences (all)	14		
Blood immunoglobulin A decreased			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Blood immunoglobulin M decreased			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Blood uric acid increased			
subjects affected / exposed	11 / 62 (17.74%)		
occurrences (all)	15		
Haemoglobin decreased			

subjects affected / exposed	57 / 62 (91.94%)		
occurrences (all)	99		
International normalised ratio increased			
subjects affected / exposed	16 / 62 (25.81%)		
occurrences (all)	18		
Lipase increased			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Lymphocyte count decreased			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	9		
Platelet count decreased			
subjects affected / exposed	54 / 62 (87.10%)		
occurrences (all)	79		
Neutrophil count decreased			
subjects affected / exposed	56 / 62 (90.32%)		
occurrences (all)	106		
Weight decreased			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
White blood cell count decreased			
subjects affected / exposed	58 / 62 (93.55%)		
occurrences (all)	108		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	12		
Fall			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	5		
Infusion related reaction			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	5		
Procedural pain			

subjects affected / exposed	11 / 62 (17.74%)		
occurrences (all)	16		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	12 / 62 (19.35%)		
occurrences (all)	12		
Tachycardia			
subjects affected / exposed	30 / 62 (48.39%)		
occurrences (all)	39		
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 62 (19.35%)		
occurrences (all)	17		
Headache			
subjects affected / exposed	46 / 62 (74.19%)		
occurrences (all)	82		
Tremor			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	17		
Lymphopenia			
subjects affected / exposed	50 / 62 (80.65%)		
occurrences (all)	80		
Splenomegaly			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	7		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Diplopia			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Photophobia			

subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	21 / 62 (33.87%)		
occurrences (all)	42		
Constipation			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	10		
Diarrhoea			
subjects affected / exposed	35 / 62 (56.45%)		
occurrences (all)	68		
Haematochezia			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	45 / 62 (72.58%)		
occurrences (all)	74		
Vomiting			
subjects affected / exposed	48 / 62 (77.42%)		
occurrences (all)	88		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Hyperbilirubinaemia			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	18		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	5		
Petechiae			
subjects affected / exposed	9 / 62 (14.52%)		
occurrences (all)	9		
Pruritus generalised			

subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	8 / 62 (12.90%)		
occurrences (all)	10		
Rash erythematous			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Rash papular			
subjects affected / exposed	8 / 62 (12.90%)		
occurrences (all)	8		
Skin lesion			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 62 (14.52%)		
occurrences (all)	12		
Back pain			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	6		
Myalgia			
subjects affected / exposed	14 / 62 (22.58%)		
occurrences (all)	19		
Neck pain			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	14 / 62 (22.58%)		
occurrences (all)	23		
Pain in jaw			

subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	7		
Infections and infestations			
Otitis media			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Respiratory syncytial virus infection			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	11 / 62 (17.74%)		
occurrences (all)	16		
Urinary tract infection			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	10		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 62 (69.35%)		
occurrences (all)	62		
Hyperglycaemia			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	8		
Hyperphosphataemia			
subjects affected / exposed	22 / 62 (35.48%)		
occurrences (all)	45		
Hyperuricaemia			
subjects affected / exposed	8 / 62 (12.90%)		
occurrences (all)	20		
Hypocalcaemia			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	11		
Hypokalaemia			

subjects affected / exposed	11 / 62 (17.74%)		
occurrences (all)	16		
Hyponatraemia			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Metabolic acidosis			
subjects affected / exposed	8 / 62 (12.90%)		
occurrences (all)	9		
Hypophosphataemia			
subjects affected / exposed	15 / 62 (24.19%)		
occurrences (all)	18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2011	The protocol was amended to modify the dose range. Pre-medication language was added to manage the site effects following T cell infusion. The packaging of the cells was re-designed to allow for the split dosing. Safety and adverse events section was updated with the DLT definition.
29 March 2012	Number of subjects was revised from 10 to 20; intra-patient dose escalation was modified as an additional safety feature; duration of administration drug is expected to persist at detectable levels in circulation for 2 weeks to 6 weeks was revised to weeks to months; pre-entry Evaluations section has been modified to add the following language: If a prior pheresis product from a CHP-784 collection and consent is used, an aliquot of this product should be used for this purpose, and not a peripheral blood specimen; enrollment and baseline assessment has been clarified that viral serologies will be based on Miller-Keystone Autologous Panel.
02 August 2012	Primary endpoints were amended with an addition of the Q-PCR testing for CART-19 vector sequences after each infusion. Study inclusion criteria was added to allow enrollment of the other high-grade NHL. Exclusion criteria was modified to exclude concurrent use of systemic steroids at the time of the cell infusion or cell collection. Treatment regimen and preparation and administration of the study drug was revised with additional guidelines for the split dosing. The tumor response assessments, safety, statistical plan were modified accordingly.
10 November 2012	Number of subjects updated from 20 to 34-40; clarified that CAR constructs would be manufactured at CHOP; Clinical data to date was updated with summary of CART19 infusions to date and GVDH risk language was added; Primary study objectives were revised as follows: Determine the safety and feasibility of administration of chimeric antigen receptor T cells transduced with the anti-CD19 lentiviral vector (referred to as "CART-19" cells), in patients who either: a) did not received a prior allogeneic SCT or had 0% residual donor engraftment ("no allo" cohort), or b) had relapsed after prior allogeneic SCT with any degree of residual donor engraftment ("allo" cohort); Study Design was updated with the revised number of patients treated; Also, it was clarified that in the first cohort 28 subjects would be included: 14 evaluable patients in the "no allo" cohort and 14 in the "allo" cohort"; Primary Study Endpoints were added; capillary leak, hypotension, GVDH (in the allo cohort only); Inclusion Criteria 1a was modified as follows: ALL without curative options for therapy, including those not eligible for allogeneic SCT because of age, comorbid disease or other contraindications to TBI-based conditioning (required for ALL SCT), lack of suitable donor or prior SCT. i) Patient could be in any complete response, or ii) Patient could have active disease but responding or stable after most recent therapy; The intent was not to enroll patients with no degree of disease control, or rapidly increasing disease burden between enrollment and cell infusion; Inclusion criteria 2 was modified as follows: Age 1 to 24 years. Patients ages 22-24 could only be enrolled if they were being treated at CHOP. Inclusion criteria 8a (have reverted to recipient hematopoiesis (no evidence of donor cells by STR analysis on 2 occasions separated by at least 1 month) was deleted

10 January 2013	Treatment Regimen added the following language: the toxicities that would preclude the next dose of T cells were DLTs of GDHD attributable to the cell infusion, and not toxicities attributable to the prior chemotherapy, such as cytopenias. A DLT prevented the infusion of the next dose, even if fully resolved by that time; CART-19 Infusion # 1 with intra-patient dosing escalation; Day 14 was modified to state that 30% of the dose could be given if no evidence for grade 3 toxicity, or higher, prolonged fever, or T cell expansion as suggested by appearance of large granual lymphocytes on the peripheral smear. Day 28 was modified to state that 60% of the dose could be given if no evidence for grade 3 toxicity, or higher, prolonged fever, or T cell expansion as suggested by appearance of large granual lymphocytes on the peripheral smear. Language to permit subsequent infusions to initiate, consolidate or extend a response was added; Day 28 evaluation; it has been clarified that the day 28 evaluation will occur regardless of whether the second dose was given or not. The day 28 evaluation was repeated 28 days after the third (60%) infusion if the patient received the infusion; Quarterly evaluations for up 2 years post infusion: RCL test (i.e. HIV-gag or VSV-G) performed at 3 and 6 months post CART-19 infusion was removed.
12 February 2013	Day 28 evaluation section was clarified that the day 28 evaluation may be repeated 28 days after the third (60%) infusion if the patient received this infusion; Tumor Response Assessments: Day 56 evaluation was removed; Accrual was deleted, as accrual had stated that accrual was anticipated to take approximately 12 months; Independent Data and Safety Monitoring Board: the number of individuals on the board was revised from four to six.
07 July 2013	Inclusion Criteria 1a was added as follows: ALL without curative options for therapy, including those not eligible for allogenic SCT because patient declined SCT (in CR3) as a therapeutic option after documented discussion about the role of SCT with a BMT physician not part of the study team; Treatment Regimen ; Day 14 regimen was replaced with Day 1 (30% of total dose). Day 28 was replaced with day 14 (60% to total dose); Packaging was revised due to the treatment regimen changes.
07 March 2014	Study title update as follows: CHP 959 – A Phase I/IIA Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCRzeta and 4-1BB Signaling Domains in Patients with Chemotherapy Resistant Or Refractory CD19+ Leukemia and Lymphoma
06 October 2014	CART-19 Infusion #1 with intra-patient dose escalation; blood sample for determination of baseline CART-19 levels obtained 20 minutes after post infusion was removed; Stopping rules related to CNS3 cohort Stopping was updated with the toxicity attribution rules; Management of toxicity section was updated with the following language: Events of Cytokine Release Syndrome (CRS) was reported and graded based on the below criteria for all patients that experienced CRS moving forward. Events prior to this amendment was reviewed and retrospectively graded and reported by the primary investigator per source documentation. The Penn Grading Scale for Cytokine Release Syndrome (PGS-CRS) was used for grading of CRS. The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (i.e. sepsis). The stop date of CRS was defined as the date when the patient had been afebrile for 24 hours and off vasopressors for 24 hours; High Dose Vasopressor Use was updated as per the new CRS criteria.
08 May 2015	Study design was updated to reflect secondary follow-up post end of study to allow for survival information and relapse free survival (as applicable); Patient withdrawal section was updated to remove patient non-compliance as a reason for premature study discontinuation. Given the nature of this investigational therapy, subjects were followed on study as long as possible for safety reasons; Data collection and follow-up section was updated to further clarify study follow-up requirements; Prior and concomitant section was updated to align with the Schedule of Study Procedures; anti-neoplastic therapies clarified requirements related to the collection of antineoplastic therapy pre- and post-CART19 infusion; Secondary Follow-up Phase was added to allow for the collection of secondary follow-up data (survival and PFS as applicable) under this protocol.

15 December 2015	Study design updated to reflect the target number of subjects to be enrolled and the maximum number of subjects to be infused under this protocol across all cohorts; Exclusion criteria #5 and #6 retired and replaced with Exclusion Criteria #13, which now aligns with the criteria in other CAR T-cell protocols; Treatment regimen Updated to reflect the maximum number of subjects to be infused under this protocol across all cohorts; Exclusion criterion #5 regarding Grade 2-4 acute or chronic GVHD was retired with protocol version 14. Consequently, the definition for Grade 2-4 GVHD provided in this section is not needed; All GVHD requiring systemic therapy was exclusionary; Topical GVHD therapy was permitted.

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: