Clinical trial results:
Phase IIIb study for relapsed/refractory pediatric/young adult acute lymphoblastic leukemia patients to be treated with CTL019

Summary

EudraCT number	2016-001991-31
Trial protocol	AT DE NO ES BE FR IT
Global end of trial date	13 October 2020

Results information

Result version number	v2 (current)
This version publication date	01 September 2021
First version publication date	28 April 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CCTL019B2001X

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03123939
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	13 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the safety of CTL019 therapy.

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	24 April 2017
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	Austria: 7
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Spain: 10
Worldwide total number of subjects	74
EEA total number of subjects	53

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)	45
Adolescents (12-17 years)	10
Adults (18-64 years)	18
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 11 study centers across 9 countries (Austria, Belgium, Canada, Germany, Spain, France, Italy, Japan, Norway).

Pre-assignment

Screening details:

This was a single arm study.

Period 1

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

Blinding implementation details:

Open-label

Arms

Arm title	CTL019

Arm description:

CTL019 transduced T cells were given as a single dose of 0.2 to 5.0 × 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 × 10^8 CTL019 transduced viable T cells (for patients > 50 kg)

Arm type	Experimental
Investigational medicinal product name	Tisagenlecleucel/Kymriah®
Investigational medicinal product code	CTL019
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

CTL019 transduced T cells were given as a single dose of 0.2 to 5.0 × 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 × 10^8 CTL019 transduced viable T cells (for patients > 50 kg)

Number of subjects in period 1	CTL019
Started	74
CTL019 infused	69
Full analysis set (FAS)	69
Cellular kinetic analysis set (CKAS)	69
Safety set (SAF)	69
Completed	33
Not completed	41
Physician decision	2
Protocol deviation	1
Death post CTL019 infusion	5

Lost to follow-up	1
Progressive disease	18
Subject/guardian decision	2
New therapy for study indication	1
Lack of efficacy	6
Discontinued prior to CTL019 infusion due to death	4
Discontinued prior CTL019 infusion: technical issue	1

Baseline characteristics

Reporting groups	
Reporting group title	CTL019
Reporting group description:	
CTL019 transduced T cells were given as a single dose of 0.2 to 5.0 × 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 × 10^8 CTL019 transduced viable T cells (for patients > 50 kg)	

Reporting group values	CTL019	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	1	1	
Children (2-11 years)	45	45	
Adolescents (12-17 years)	10	10	
Adults (18-64 years)	18	18	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
included only those participants who received an infusion of CTL019			
Units: years			
arithmetic mean	11.3		
standard deviation	± 6.72	-	
Sex: Female, Male Units: Participants			
Female	30	30	
Male	44	44	
Race/Ethnicity, Customized Units: Subjects			
White	55	55	
Black or African American	2	2	
Asian	4	4	
American Indian or Alaska Native	1	1	
Unknown	3	3	
Other	9	9	

End points

End points reporting groups

Reporting group title	CTL019

Reporting group description:

CTL019 transduced T cells were given as a single dose of 0.2 to 5.0 × 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 × 10^8 CTL019 transduced viable T cells (for patients > 50 kg)

Primary: Number of participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of participants with Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

Treatment emergent adverse events were collected from CTL019 infusion until end of study, up to 12 months.

End point type	Primary

End point timeframe:

From CTL019 infusion until end of study, up to 12 months

Notes:

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

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69[2]			
Units: Participants	69			

Notes:

[2] - Only the participants who received the CTL019 infusion were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieved CR or CRi at Month 6 without Stem Cell Transplantation (SCT)

End point title	Number of participants who achieved CR or CRi at Month 6 without Stem Cell Transplantation (SCT)

End point description:

Proportion of participants who achieved CR or CRi at Month 6 without stem cell transplantation between CTL019 infusion and Month 6 response assessment

End point type	Secondary

End point timeframe:

Month 6

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants	41			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Remission Rate (ORR)

End point title	Overall Remission Rate (ORR)

End point description:

ORR is defined as the proportion of participants with a best overall disease response of Complete remission (CR) or CR with incomplete blood count recovery (CRi), where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until Month 6.

End point type	Secondary

End point timeframe:

From CTL019 infusion until Month 6

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants	57			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieved CR or CRi and then proceeded to Stem Cell Transplantation (SCT) while in remission before Month 6 assessment

End point title	Number of participants who achieved CR or CRi and then proceeded to Stem Cell Transplantation (SCT) while in remission before Month 6 assessment

End point description:

Proportion of participants who achieved CR or CRi and then proceeded to stem cell transplantation while in remission prior to Month 6 response assessment.

End point type	Secondary

End point timeframe:

From CTL019 infusion until Month 6

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

DOR is the duration of remission from the date when the response criteria of CR or CRi was first met post CTL019 infusion to the date of relapse or death due to acute lymphoblastic leukemia (ALL), whichever occured first.

End point type	Secondary

End point timeframe:

Actual reported Time Frame: up to 14.4 months post CTL019 infusion (planned follow-up period per protocol was only 12 months post CTL019 infusion)

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Months				
median (full range (min-max))	8.9 (1.7 to 14.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival (EFS)

End point title	Event-free survival (EFS)

End point description:

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

End point type	Secondary

End point timeframe:

Actual reported Time Frame: up to 15.1 months post CTL019 infusion (planned follow-up period per protocol was only 12 months post CTL019 infusion)

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Months				
median (full range (min-max))	8.97 (0.0 to 15.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free survival (RFS)

End point title	Relapse-free survival (RFS)

End point description:

RFS is measured by the time from achievement of CR or CRi whichever occured first post CTL019 infusion, to relapse or death due to any cause during CR or CRi.

End point type	Secondary

End point timeframe:

Actual reported Time Frame: up to 14.4 months post CTL019 infusion (planned follow-up period per protocol was only 12 months post CTL019 infusion)

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Months				
median (full range (min-max))	8.9 (1.7 to 14.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

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

End point type	Secondary

End point timeframe:

Actual reported Time Frame: up to 24.4 months post CTL019 infusion (planned follow-up period per protocol was only 12 months post CTL019 infusion)

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Months				
median (full range (min-max))	11.7 (0.3 to 24.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who attained CR or CRi at Day 28 by baseline bone marrow tumor burden

End point title	Number of participants who attained CR or CRi at Day 28 by baseline bone marrow tumor burden

End point description:

Proportion of participants who attained CR or CRi at Day 28 post CTL019 infusion by baseline bone marrow tumor burden.

End point type	Secondary

End point timeframe:

Day 28

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Participants				
Low tumor burden (morphologic result < 50%)	26			
High tumor burden (morphologic result ≥ 50%)	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who attained CR or CRi at Day 28

End point title	Number of participants who attained CR or CRi at Day 28

End point description:

Proportion of participants who attained CR or CRi at Day 28 post CTL019 infusion.

End point type	Secondary

End point timeframe:

Day 28

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants	59			

Statistical analyses

No statistical analyses for this end point

Secondary: Bone marrow Minimum Residual Disease (MRD) status by flow cytometry on Day 28 post CTL019 infusion

End point title	Bone marrow Minimum Residual Disease (MRD) status by flow cytometry on Day 28 post CTL019 infusion

End point description:

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods. The most frequently used methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and polymerase chain reaction (PCR) assays to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes or fusion transcripts (e.g. BCR-ABL (Philadelphia chromosome)). The results include the descriptive summary of MRD qualitative result (positive/negative) before treatment and at Day 28 after treatment and before HSCT by local assessment (flow cytometry).

End point type	Secondary

End point timeframe:

Enrollment/Pre-chemotherapy and Day 28

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants				
Enrollment/Pre-Chemotherapy|Negative	0			
Day 28|Negative	44			
Enrollment/Pre-Chemotherapy|Positive	51			
Day 28|Positive	4			
Enrollment/Pre-Chemotherapy|Unknown	4			
Day 28|Unknown	2			
Enrollment/Pre-Chemotherapy|Not done	1			
Day 28|Not done	0			
Enrollment/Pre-Chemotherapy|Missing	13			
Day 28|Missing	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Bone marrow Minimum Residual Disease (MRD) status by qPCR on Day 28 post CTL019 infusion

End point title	Bone marrow Minimum Residual Disease (MRD) status by qPCR on Day 28 post CTL019 infusion

End point description:

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods. The most frequently used methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and polymerase chain reaction (PCR) assays to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes or fusion transcripts (e.g. BCR-ABL (Philadelphia chromosome)). The results include the descriptive summary of MRD qualitative result (positive/negative) before treatment and at Day 28 after treatment and before HSCT by local assessment (qPCR).

End point type	Secondary

End point timeframe:

Enrollment/Pre-chemotherapy and Day 28

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants				
Enrollment/Pre-Chemotherapy|Negative	1			
Day 28|Negative	31			
Enrollment/Pre-Chemotherapy|Positive	32			
Day 28|Positive	3			
Enrollment/Pre-Chemotherapy|Unknown	4			
Day 28|Unknown	0			
Enrollment/Pre-Chemotherapy|Not done	0			
Day 28|Not done	0			
Enrollment/Pre-Chemotherapy|Missing	32			
Day 28|Missing	35			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of immunogenicity against CTL019 - Humoral immunogenicity

End point title	Incidence of immunogenicity against CTL019 - Humoral immunogenicity

End point description:

The humoral immunogenicity assessment included evaluation of pre-existing (pre-treatment) and post-treatment anti-CTL019 antibodies to examine the incidence of immunogenicity with treatment.

End point type	Secondary

End point timeframe:

Baseline, Day 14, Day 28, Month 3, Month 6 and Month 12

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants				
Baseline|Positive	62			
Day 14|Positive	53			
Day 28|Positive	50			
Month 3|Positive	53			
Month 6|Positive	44			
Month 12|Positive	32			
Baseline|Negative	7			
Day 14|Negative	14			
Day 28|Negative	13			
Month 3|Negative	5			
Month 6|Negative	4			
Month 12|Negative	1			
Baseline|Missing	0			
Day 14|Missing	2			
Day 28|Missing	6			
Month 3|Missing	11			
Month 6|Missing	21			
Month 12|Missing	36			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of immunogenicity against CTL019 - Cellular Immunogenicity

End point title	Incidence of immunogenicity against CTL019 - Cellular Immunogenicity

End point description:

The cellular immunogenicity assessment included percentage of CD4+ and CD8+ T- cells specific for CTL019.

End point type	Secondary

End point timeframe:

Baseline, Day 14, Day 28, Month 3, Month 6 and Month 12

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Participants				
CTL019 Pool 1 CD3+ CD4+ IFNg+ Baseline	69			
CTL019 Pool 1 CD3+ CD4+ IFNg+ Day 14	65			
CTL019 Pool 1 CD3+ CD4+ IFNg+ Day 28	63			
CTL019 Pool 1 CD3+ CD4+ IFNg+ Month 3	58			
CTL019 Pool 1 CD3+ CD4+ IFNg+ Month 6	51			
CTL019 Pool 1 CD3+ CD4+ IFNg+ Month 12	34			
CTL019 Pool 2 CD3+ CD4+ IFNg+ Baseline	69			
CTL019 Pool 2 CD3+ CD4+ IFNg+ Day 14	65			
CTL019 Pool 2 CD3+ CD4+ IFNg+ Day 28	63			
CTL019 Pool 2 CD3+ CD4+ IFNg+ Month 3	58			
CTL019 Pool 2 CD3+ CD4+ IFNg+ Month 6	51			
CTL019 Pool 2 CD3+ CD4+ IFNg+ Month 12	34			
CTL019 Pool 1 CD3+ CD8+ IFNg+ Baseline	69			
CTL019 Pool 1 CD3+ CD8+ IFNg+ Day 14	65			
CTL019 Pool 1 CD3+ CD8+ IFNg+ Day 28	63			
CTL019 Pool 1 CD3+ CD8+ IFNg+ Month 3	58			
CTL019 Pool 1 CD3+ CD8+ IFNg+ Month 6	51			
CTL019 Pool 1 CD3+ CD8+ IFNg+ Month 12	34			
CTL019 Pool 2 CD3+ CD8+ IFNg+ Baseline	69			
CTL019 Pool 2 CD3+ CD8+ IFNg+ Day 14	65			
CTL019 Pool 2 CD3+ CD8+ IFNg+ Day 28	63			
CTL019 Pool 2 CD3+ CD8+ IFNg+ Month 3	58			
CTL019 Pool 2 CD3+ CD8+ IFNg+ Month 6	51			
CTL019 Pool 2 CD3+ CD8+ IFNg+ Month 12	34			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-28d: PK parameters for CTL019 by qPCR

End point title	AUC0-28d: PK parameters for CTL019 by qPCR

End point description:

Area under the concentration-time curve of CTL019 in the peripheral blood after single dose administration from time zero to Day 28 after single dose administration as measured by qPCR.

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: copies/ug*day				
geometric mean (geometric coefficient of variation)	365000 (± 174.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-84d: PK parameters for CTL019 by qPCR

End point title	AUC0-84d: PK parameters for CTL019 by qPCR

End point description:

Area under the concentration-time curve of CTL019 in the peripheral blood after single dose administration from time zero to Day 84 after single dose administration as measured by qPCR.

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28 and 84

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Copies/ug*day				
geometric mean (geometric coefficient of variation)	555000 (± 193.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: PK parameters for CTL019 by qPCR

End point title	Cmax: PK parameters for CTL019 by qPCR

End point description:

The maximum (peak) observed in peripheral blood drug concentration after single dose administration

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28, Month 3, 6, 9 and 12

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: copies/ug				
geometric mean (geometric coefficient of variation)	35300 (± 215.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clast: PK parameters for CTL019 by qPCR

End point title	Clast: PK parameters for CTL019 by qPCR

End point description:

The last observed in peripheral blood drug concentration after single dose administration.

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28, Month 3, 6, 9 and 12

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: copies/ug				
geometric mean (geometric coefficient of variation)	240 (± 147.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: PK parameters for CTL019 by qPCR

End point title	Tmax: PK parameters for CTL019 by qPCR

End point description:

The time to reach maximum (peak) peripheral blood drug concentration after single dose administration.

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28, Month 3, 6, 9 and 12

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: days				
median (full range (min-max))	10.0 (5.86 to 17.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: T1/2: PK parameters for CTL019 by qPCR

End point title	T1/2: PK parameters for CTL019 by qPCR

End point description:

The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood.

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28, Month 3, 6, 9 and 12

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: days				
geometric mean (geometric coefficient of variation)	63.8 (± 182.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tlast: PK parameters for CTL019 by qPCR

End point title	Tlast: PK parameters for CTL019 by qPCR

End point description:

The time to reach the last observed quantifiable concentration in peripheral blood after single dose administration.

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28, Month 3, 6, 9 and 12

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: days				
median (full range (min-max))	269 (12.9 to 379)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-28d by maximum Cytokine Release Syndrome (CRS) grade

End point title	AUC0-28d by maximum Cytokine Release Syndrome (CRS) grade

End point description:

AUC0-28d from time zero to Day 28 after single dose administration as measured by qPCR. PK results were presented by the maximum Penn Grading Scale (Grade 1 to 4):
1 - Mild reaction
2 - Moderate reaction
3 - More severe reaction
4 - Life-threatening complications

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: copies/ug*day				
geometric mean (geometric coefficient of variation)				
No CRS	141000 (± 130.6)			
Grade 1/2	374000 (± 72.6)			
Grade 3	643000 (± 272.8)			
Grade 4	890000 (± 119.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax by maximum Cytokine Release Syndrome (CRS) grade

End point title	Cmax by maximum Cytokine Release Syndrome (CRS) grade

End point description:

The maximum (peak) observed in peripheral blood drug concentration after single dose administration. PK results were presented by the maximum Penn Grading Scale (Grade 1 to 4):
1 - Mild reaction
2 - Moderate reaction
3 - More severe reaction
4 - Life-threatening complications

End point type	Secondary

End point timeframe:

Day 1 10 min post-infusion, Day 4, 7, 11, 14, 28, Month 3, 6, 9 and 12

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: copies/ug				
geometric mean (geometric coefficient of variation)				
No CRS	16300 (± 157.8)			
Grade 1/2	31200 (± 199.3)			
Grade 3	66600 (± 299.9)			
Grade 4	87900 (± 84.9)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Total number of deaths

End point title	Total number of deaths

End point description:

Deaths were reported in the pre-treatment period (without receiving a CTL019 infusion) and post-treatment period (after receiving a CTL019 infusion).

End point type	Post-hoc

End point timeframe:

Pre-treatment period: up to 81 days post signed informed consent; Post-treatment period: up to 24.4 months post CTL019 infusion (planned follow-up period per protocol was only 12 months post CTL019 infusion)

End point values	CTL019			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Participants				
Pre-treatment (without CTL019 infusion)	4			
Post-treatment: ≤30 days (after CTL019 infusion)	4			
Post-treatment: >30 days (after CTL019 infusion)	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from CTL019 infusion, until approximately 12 months post infusion. For all-cause mortality, the data are presented from CTL019 infusion up to 24.4 months post infusion.

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	23.1

Reporting groups

Reporting group title	CTL019

Reporting group description:

Included all the participants who received CTL019 infusion

Serious adverse events	CTL019		
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 69 (72.46%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
B precursor type acute leukaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neoplasm progression			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 69 (15.94%)		
occurrences causally related to treatment / all	9 / 16		
deaths causally related to treatment / all	0 / 0		
Drug withdrawal syndrome			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cytokine release syndrome			
subjects affected / exposed	28 / 69 (40.58%)		
occurrences causally related to treatment / all	28 / 28		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Completed suicide			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Irritability			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood fibrinogen decreased			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest X-ray abnormal			

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immunoglobulins decreased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Splinter				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Left ventricular dysfunction				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Depressed level of consciousness				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Dyskinesia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Facial paralysis				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bone marrow failure				

subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatosplenomegaly			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint effusion			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Alternaria infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Aspergillus infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Candida infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis orbital			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Central nervous system infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral fungal infection			

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enterococcal infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	3 / 69 (4.35%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis aseptic				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Periorbital cellulitis				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia haemophilus				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 69 (4.35%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 69 (1.45%)			
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 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypernatraemia				

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	CTL019		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 69 (95.65%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	8		
Hypertension			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	8		
General disorders and administration site conditions			

Face oedema subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 6 4 / 69 (5.80%) 4 24 / 69 (34.78%) 43 5 / 69 (7.25%) 5 5 / 69 (7.25%) 6 7 / 69 (10.14%) 9		
Immune system disorders Allergy to immunoglobulin therapy subjects affected / exposed occurrences (all) Hypogammaglobulinaemia subjects affected / exposed occurrences (all) Cytokine release syndrome subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5 21 / 69 (30.43%) 22 30 / 69 (43.48%) 35		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Hypoxia	8 / 69 (11.59%) 8 14 / 69 (20.29%) 22		

subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	10		
Nasal congestion			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	6		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Insomnia			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	6		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	10		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	11		
Blood fibrinogen decreased			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Immunoglobulins decreased			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	11 / 69 (15.94%)		
occurrences (all)	26		
Lymphocyte count decreased			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	6		
Platelet count decreased			

subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	18		
White blood cell count decreased			
subjects affected / exposed	14 / 69 (20.29%)		
occurrences (all)	23		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Tachycardia			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	10		
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 69 (23.19%)		
occurrences (all)	18		
Seizure			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Anaemia			
subjects affected / exposed	14 / 69 (20.29%)		
occurrences (all)	26		
Thrombocytopenia			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	13		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Constipation			

subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 10		
Abdominal pain subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 13		
Diarrhoea subjects affected / exposed occurrences (all)	17 / 69 (24.64%) 24		
Vomiting subjects affected / exposed occurrences (all)	13 / 69 (18.84%) 17		
Nausea subjects affected / exposed occurrences (all)	16 / 69 (23.19%) 20		
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 5		
Erythema subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 8		
Rash subjects affected / exposed occurrences (all)	10 / 69 (14.49%) 12		
Pruritus subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 8		
Petechiae subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 7		
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 10		
Back pain subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 7		
Myalgia subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 6		
Pain in extremity subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 13		
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 6		
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 69 (13.04%) 9		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 9		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Decreased appetite subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 8		
Hypocalcaemia subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 9		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 8		
Hyperuricaemia			

subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	14 / 69 (20.29%)		
occurrences (all)	20		
Hypomagnesaemia			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	7		
Hypophosphataemia			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2017	At the time of this protocol amendment, 2 sites had been initiated and 1 patient had been enrolled. The protocol was amended mainly to change the study designation from a Phase II expanded treatment program to a Phase IIIb interventional clinical study protocol, to clarify how CRS should be managed in Japan, and to update various sections of the protocol to align with the clinical development program for CTL019.
09 January 2018	At the time of this protocol amendment, 9 sites had been initiated in Europe and Canada, 15 patients had been enrolled and 7 patients infused. The protocol was amended mainly to institute updates to allow enrollment of patients previously treated with blinatumomab. Pre-treatment with blinatumomab is being allowed as this is the only other CD19-targeted therapy approved for the population of patients being assessed in this study.
02 October 2018	- To amend age inc criterion from "age 3 years at time of Screening to age 21 years at time of initial diagnosis" to remove lower age limit of ≥ 3 years old at time of Screening and to limit upper age limit to < 26 years at Screening in line with authorized product label for CTL019 for pediatric and young adult patients with r/r B-cell ALL. - To amend inc criterion to revise timing of CTL019 infusion after allogenic stem cell transplantation (SCT) from ≥ 6 months to ≥ 4 months, and to add timing of leukapheresis for CTL019 manufacturing to be performed at least 12 weeks following allogenic SCT. - To amend hepatic function inc criterion to add AST upper limit, and to add exception for patients with Gilbert's syndrome. - To amend serology exc criteria to clarify that testing must be repeated if interval between Screening and infusion is greater than 8 weeks. - To amend cardiology exc criterion to elaborate on specific types of cardiac abnormalities excluded. - To amend pregnancy exc criterion to clarify that serum pregnancy test is required prior to infusion, and to re-order so it is next to contraception criterion. - To remove analysis of adverse events of special interest (AESIs) as AESIs are not part of study objectives for this Phase 3b study. All AEs were collected and reported in accordance with clinical development program for CTL019. Therefore, removing terminology/text related to AESIs did not exclude events from overall AE reporting. - To increase projected no. of enrolled patients from approximately 55 patients to approximately 70 patients based on current recruitment rate. - To amend relevant wording on patient withdrawal to reflect EEA GDPR requirements. - To describe guidance for handling of patients undergoing a repeat manufacture of CTL019 cells in case of initial manufacture failure. - To amend censoring reason for new anticancer therapy to allow for reinfusion of CTL019.

06 August 2019	- Include further details on requirements for leukapheresis due to fact that separate leukapheresis study was completing and leukapheresis procedure was incorporated in this study - Update CRS treatment algorithm to align with approved algorithm in SmPC including permission of up to 4 doses of tocilizumab in addition to moving siltuximab under alternative measures. - To delete Japan-specific CRS treatment algorithm as updated CRS treatment algorithm now covers all possible treatment scenarios for all countries. - To clarify rationale for information provided on approach for out of specification CTL019. - To clarify SAE reporting requirements for grade ≥ 4 neurotoxicities and deaths. - To increase projected number of patients from approximately 70 to approximately 80 patients. - To remove inc criterion no. 4 to align with approved label in all regions. - To amend inc criterion no. 11 to add note about prohibited concomitant medications and washout times. - To add new inc criterion describing inc of patients with active CNS leukemia involvement - To update background details on clinical efficacy and safety of CTL019. - To update background details and guidance on management of potential and identified safety risks. - To update serology test requirements. - To reduce frequency of laboratory assessments. Further clarification on rationale in Protocol Amendment 3 for including patients less than 3 years of age in this study was included as follows: - FDA and EMA approval of CTL019 in pediatric/young adult patients with r/r B-ALL allows patients up to 25 years of age to be treated, and as it did not restrict lower age limit, includes patients less than 3 years old.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported