Clinical trial results:
A phase II, open label, multi-center trial to determine the efficacy and safety of tisagenlecleucel re-infusion in Pediatric and Adolescent Young Adult (AYA) patients with acute lymphoblastic leukemia experiencing loss of B cell aplasia

Summary

EudraCT number	2021-001535-99
Trial protocol	Outside EU/EEA
Global end of trial date	19 October 2021

Results information

Result version number	v1 (current)
This version publication date	30 April 2022
First version publication date	30 April 2022

Trial information

Trial identification

Sponsor protocol code	CCTL019BUS03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04225676
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the incidence of B-cell aplasia after re-infusion of tisagenlecleucel.

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	19 October 2020
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	United States: 5
Worldwide total number of subjects	5
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	2
Adolescents (12-17 years)	2
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were 7 participants screened.

Period 1

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

Arms

Arm title	Tisagenlecleucel

Arm description:

Tisagenlecleucel Cell Dispersion for Infusion given once during the study. The approved dose range for tisagenlecleucel is: 0.2 to 5.0×10^6 CAR positive viable T cells / kg for patients' ≤ 50 kg body weight or 0.1 to 2.5×10^8 CAR-positive viable T cells for patients > 50 kg body weight.

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

Dosage and administration details:

A second dose (for reinfusion) of commercial tisagenlecleucel was not considered investigation treatment because it was released commercially when prescribed by the treating physician in the course of medical practice.

Number of subjects in period 1	Tisagenlecleucel
Started	5
Full analysis, safety and enrolled sets	5
Completed	0
Not completed	5
Physician decision	1
Study terminated by sponsor	3
Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	Tisagenlecleucel

Reporting group description:

Tisagenlecleucel Cell Dispersion for Infusion given once during the study. The approved dose range for tisagenlecleucel is: 0.2 to 5.0×10^6 CAR positive viable T cells / kg for patients' ≤ 50 kg body weight or 0.1 to 2.5×10^8 CAR-positive viable T cells for patients > 50 kg body weight.

Reporting group values	Tisagenlecleucel	Total	
Number of subjects	5	5	
Age Categorical Units: Participants			
< 10 years	2	2	
>=10 to <18 years	2	2	
>=18 years	1	1	
Sex: Female, Male Units: participants			
Female	1	1	
Male	4	4	
Race Units: Subjects			
White	5	5	

Subject analysis sets

Subject analysis set title	Best responses reported
Subject analysis set type	Full analysis

Subject analysis set description:

1 = CR = Complete remission and 2 = CRi = Complete remission without complete blood count recovery

Reporting group values	Best responses reported		
Number of subjects	5		
Age Categorical Units: Participants			
< 10 years >=10 to <18 years >=18 years			
Sex: Female, Male Units: participants			
Female Male			
Race Units: Subjects			
White	5		

End points

End points reporting groups

Reporting group title	Tisagenlecleucel

Reporting group description:

Tisagenlecleucel Cell Dispersion for Infusion given once during the study. The approved dose range for tisagenlecleucel is: 0.2 to 5.0×10^6 CAR positive viable T cells / kg for patients' ≤ 50 kg body weight or 0.1 to 2.5×10^8 CAR-positive viable T cells for patients > 50 kg body weight.

Subject analysis set title	Best responses reported
Subject analysis set type	Full analysis

Subject analysis set description:

1 = CR = Complete remission and 2 = CRi = Complete remission without complete blood count recovery

Primary: Percentage of patients who establish B cell aplasia within 9 months of reinfusion

End point title	Percentage of patients who establish B cell aplasia within 9 months of reinfusion[1]

End point description:

Percentage of patients who establish B-cell aplasia at any visit following re-infusion with tisagenlecleucel. B-cell aplasia is defined as peripheral blood (PB) absolute B lymphocyte count <50/µL. Planned timeframe was 12 months but actual timeframe was approximately 9 months due to early termination of the trial. Day 1 is post lymphodepleting chemotherapy and pre-reinfusion of tisagenlecleucel.

End point type	Primary

End point timeframe:

Post-reinfusion up to 9 months (Day 1 is excluded)

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 done

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Participants	2			

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 percentage of participants with a best overall disease response of complete remission (CR) or CR with incomplete blood count recovery (CRi). However, the rate was not calculated due to low enrollment. Participants' best responses have been listed by day in study with 1=Complete response (CR) and 2= CRi = CR with incomplete blood count recovery.

End point type	Secondary

End point timeframe:

Post-reinfusion up to 9 months

End point values	Best responses reported			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Day				
Participant A - Day 34	1			
Participant A - Day 67	1			
Participant B - Day 24	2			
Participant C - Day 32	1			
Participant C - Day 91	2			
Participant C - Day 182	1			
Participant C - Day 274	2			
Participant D - Day 29	1			
Participant D - Day 84	2			
Participant D - Day 177	2			
Participant D - Day 211	2			
Participant E - Day 28	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Event free survival (EFS)

End point title	Event free survival (EFS)

End point description:

Time from reinfusion to the earliest of the following: death from any cause after remission, relapse, treatment failure (defined as no response in the study or discontinuation from the study for death, adverse event, lack of efficacy or progressive disease or new cancer therapy).

End point type	Secondary

End point timeframe:

Reinfusion up to 9 months

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Days	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Time from date of re-infusion to the date of death due to any reason.

End point type	Secondary

End point timeframe:

Reinfusion up to 9 months

End point values	Tisagenlecleucel			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Days	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study for a duration of 274 days.

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Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	All@subjects

Reporting group description:

All@subjects

Serious adverse events	All@subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome			

subjects affected / exposed	1 / 5 (20.00%)		
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@subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer fatigue			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Investigations			
Enterovirus test positive			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	3		
Neutrophil count decreased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Human rhinovirus test positive			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respirovirus test positive			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Dental caries			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	3		
Tooth development disorder			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Rash			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 3 / 5 (60.00%) 4		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) HCoV-OC43 infection subjects affected / exposed occurrences (all) Paronychia subjects affected / exposed occurrences (all) Polyomavirus viraemia subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 2 1 / 5 (20.00%) 1		
Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 3 / 5 (60.00%) 4 1 / 5 (20.00%) 1 1 / 5 (20.00%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2020	The amendment was implemented prior to first patient screened or enrolled. It was amended to clarify that tisagenlecleucel would not be supplied as an investigational product. Participants in the study, who had an additional commercial dose available, were to be prescribed commercial tisagenlecleucel by a physician and it was to be administered in the course of medical practice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported