



Clinical trial results:

A Phase II, single arm, multicenter, open-label trial to determine the safety and efficacy of tisagenlecleucel in pediatric patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma (BIANCA)

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 | 2017-005019-15 |
| Trial protocol | ES FR DE SE DK NO AT GB NL FI IT |
| Global end of trial date | 26 April 2023 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 10 November 2023 |
| First version publication date | 10 November 2023 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CCTL019C2202 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03610724 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001654-PIP02-17 |

| | |
|--|-----|
| 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 | 26 April 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 April 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of tisagenlecleucel therapy as measured by ORR and determined by local investigator assessments in subjects with aggressive r/r B-cell NHL.

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 February 2019 |
| 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 | Australia: 2 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Japan: 4 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Norway: 2 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | United Kingdom: 4 |

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | United States: 7 |
| Worldwide total number of subjects | 33 |
| EEA total number of subjects | 14 |

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) | 11 |
| Adolescents (12-17 years) | 18 |
| Adults (18-64 years) | 4 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in twenty-four centers across 14 countries. Although 34 participants met the eligibility criteria and apheresis was accepted by the manufacturing facility, only 33 were infused in the study.

Pre-assignment

Screening details:

Consent, Screening, Pre-treatment, Treatment and Follow-up. In the Pretreatment phase, the subject may have undergone optional bridging therapy or lymphodepleting chemotherapy.

Full Analysis Set: 33

Efficacy Analysis Set (EAS): 28; 4 patients with Complete Response prior to infusion & 1 without a scan prior to infusion excluded from EAS.

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:

These participants were infused once with CAR-positive viable T cells.

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

Dosage and administration details:

Tisagenlecleucel was administered once as an intravenous infusion, at a dose of either 0.2 to 5 x 10⁶ CAR-positive viable T cells per kg body weight for subjects ≤ 50 kg or 0.1 to 2.5 x 10⁸ CARpositive viable T cells for subjects > 50 kg

| | |
|--|------------------------------|
| Investigational medicinal product name | lymphodepleting chemotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

lymphodepletion with recommended Fludarabine (30 mg/m² IV daily for 4 days) and cyclophosphamide (500 mg/m² IV daily for 2 days starting with the first dose of fludarabine) (unless contra-indicated for subject)

| | |
|--|------------------------|
| Investigational medicinal product name | Bridging Therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Pre-treatment phase could also include bridging therapy of investigator's choice

| Number of subjects in period 1 | Tisagenlecleucel |
|---|------------------|
| Started | 33 |
| Met Eligibility criteria and were infused | 33 |
| Met Eligibility criteria, not infused* | 1 |
| Completed treatment & primary f/u phase | 14 |
| Discont. treatment & primary f/u phase | 19 |
| Completed | 14 |
| Not completed | 19 |
| Adverse event, serious fatal | 17 |
| Physician decision | 1 |
| Lost to follow-up | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Tisagenlecleucel |
|-----------------------|------------------|

Reporting group description:

These participants were infused once with CAR-positive viable T cells.

| Reporting group values | Tisagenlecleucel | Total | |
|----------------------------|------------------|-------|--|
| Number of subjects | 33 | 33 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 11 | 11 | |
| Adolescents (12-17 years) | 18 | 18 | |
| Adults (18-64 years) | 4 | 4 | |
| Age Continuous | | | |
| Units: years | | | |
| median | 12.8 | | |
| standard deviation | ± 4.98 | - | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 10 | 10 | |
| Male | 23 | 23 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 28 | 28 | |
| Black or African American | 1 | 1 | |
| Asian | 2 | 2 | |
| Missing | 2 | 2 | |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Tisagenlecleucel |
| Reporting group description: These participants were infused once with CAR-positive viable T cells. | |

Primary: Overall response rate (ORR) as determined by local investigator

| | |
|-----------------|--|
| End point title | Overall response rate (ORR) as determined by local investigator ^[1] |
|-----------------|--|

End point description:

The overall response rate (ORR) is defined as the percentage of subjects with a best overall disease response of complete response (CR) or partial response (PR), where the best overall disease response is defined as the best disease response recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever comes first.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

any time post-tisagenlecleucel infusion until progressive disease, start of new anticancer therapy, discontinuation or end of study (2 years after last patient first visit), up to 4 years

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 | 28 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 32.1 (15.9 to 52.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Event free survival (EFS)

| | |
|-----------------|---------------------------|
| End point title | Event free survival (EFS) |
|-----------------|---------------------------|

End point description:

Event free survival (EFS) is defined as the time from date of first tisagenlecleucel infusion to the earliest date of death from any cause, disease progression as determined by local investigator assessments, or starting new anticancer therapy for underlying cancer, excluding hematopoietic stem cell transplant (HSCT).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through study completion, up to 4 years

| | | | | |
|----------------------------------|------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.1 (1.1 to 2.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

| | |
|--|----------------------------|
| End point title | Duration of response (DOR) |
| End point description: | |
| Duration of response (DOR) is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented progression or death due to underlying cancer. | |
| End point type | Secondary |
| End point timeframe: | |
| Through study completion, up to 4 years | |

| | | | | |
|----------------------------------|------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9 (1.0 to 999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

| | |
|--|---------------------------------|
| End point title | Progression free survival (PFS) |
| End point description: | |
| Progression free survival (PFS) is defined as the time from the date of first tisagenlecleucel infusion to the date of first documented disease progression as determined by local investigator assessments or death due to any cause. | |
| End point type | Secondary |
| End point timeframe: | |
| Through study completion, up to 4 years | |

| End point values | Tisagenlecleucel | | | |
|----------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.5 (1.1 to 2.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse free survival (RFS)

| | |
|---|-----------------------------|
| End point title | Relapse free survival (RFS) |
| End point description: Relapse free survival (RFS) is defined as the time from the date of first documented disease response (CR or PR) as determined by local investigator assessments to the date of first documented disease progression or death due to any cause. | |
| End point type | Secondary |
| End point timeframe: Through study completion, up to 4 years | |

| End point values | Tisagenlecleucel | | | |
|----------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9 (1.0 to 999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

| | |
|--|-----------------------|
| End point title | Overall survival (OS) |
| End point description: Overall survival (OS) is defined as the time from date of first tisagenlecleucel infusion to the date of death due to any cause. | |
| End point type | Secondary |
| End point timeframe: Through study completion, up to 4 years | |

| | | | | |
|----------------------------------|-------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.4 (3.4 to 999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: Tlast

| | |
|--|------------------------------------|
| End point title | Cellular kinetics parameter: Tlast |
| End point description: The time of last observed quantifiable transgene level in peripheral blood. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted. | |
| End point type | Secondary |
| End point timeframe: Through study completion, up to 4 years | |

| | | | | |
|-------------------------------|---------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: days | | | | |
| median (full range (min-max)) | 40.0 (13.0 to 1090) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: Tmax

| | |
|--|-----------------------------------|
| End point title | Cellular kinetics parameter: Tmax |
| End point description: The time to reach maximum (peak) transgene level (days) in peripheral blood or other body fluid after single dose administration. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted. | |
| End point type | Secondary |

End point timeframe:

Through study completion, up to 4 years

| | | | | |
|-------------------------------|---------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: days | | | | |
| median (full range (min-max)) | 12.7 (1.90 to 21.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of pre-existing and treatment induced humoral immunogenicity and cellular immunogenicity against tisagenlecleucel cellular kinetics, safety and efficacy

| | |
|-----------------|---|
| End point title | Levels of pre-existing and treatment induced humoral immunogenicity and cellular immunogenicity against tisagenlecleucel cellular kinetics, safety and efficacy |
|-----------------|---|

End point description:

The humoral immunogenicity assay measures the antibody titers specific to tisagenlecleucel prior to and following infusion by flow cytometry. A subject was only defined as positive for tisagenlecleucel treatment-induced or -boosted anti-mCAR19 antibodies when the anti-mCAR19 antibody median fluorescence intensity at any time post-infusion was at least 2.28-fold higher (for samples analyzed on or prior to 05-May-2021) or 2.38-fold higher (for samples analyzed on or after 06-May-2021) than pre-infusion levels for participants whose baseline status was positive (boosted) or if the baseline status was negative but any post-baseline interpretation was positive (induced).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Until disease progression or through study completion, up to 4 years

| | | | | |
|--|------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| anti-tisagenlecleucel antibodies (+ve) at baseline | 87.9 | | | |
| anti-tisa antibodies (+ve) anytime post-baseline | 97.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: Clast

| | |
|-----------------|------------------------------------|
| End point title | Cellular kinetics parameter: Clast |
|-----------------|------------------------------------|

End point description:

The last observed quantifiable transgene level in peripheral blood. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through study completion, up to 4 years

| End point values | Tisagenlecleucel | | | |
|---|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: copies/ μ g | | | | |
| geometric mean (geometric coefficient of variation) | 344 (\pm 350.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: AUC0-28d

| | |
|-----------------|---------------------------------------|
| End point title | Cellular kinetics parameter: AUC0-28d |
|-----------------|---------------------------------------|

End point description:

Area Under the Concentration-time Curve (AUs) from the time course of transgene levels in peripheral blood following tisagenlecleucel infusion (days*copies/ μ g), from day of infusion to day 28. D28 refers to the timepoint for definition of responder populations. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through study completion, up to 4 years

| End point values | Tisagenlecleucel | | | |
|---|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: copies/ μ g*days | | | | |
| geometric mean (geometric coefficient of variation) | 53500 (\pm 154.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cellular kinetics parameter: Cmax

| | |
|-----------------|-----------------------------------|
| End point title | Cellular kinetics parameter: Cmax |
|-----------------|-----------------------------------|

End point description:

The maximum (peak) transgene level (copies/μg) observed in peripheral blood or other body fluid after single dose administration as measured by qPCR. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted. Pharmacokinetics of tisagenlecleucel were based on chimeric antigen receptor (CAR) transgene levels in peripheral blood as detected by qPCR, unless otherwise noted.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through study completion, up to 4 years

| | | | | |
|---|------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: copies/μg | | | | |
| geometric mean (geometric coefficient of variation) | 5140 (± 238.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who proceeded to stem cell transplant (SCT) after tisagenlecleucel infusion

| | |
|-----------------|--|
| End point title | Percentage of participants who proceeded to stem cell transplant (SCT) after tisagenlecleucel infusion |
|-----------------|--|

End point description:

These participants proceeded to transplant any time post-tisagenlecleucel therapy until end of study (EOS).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through study completion, up to 4 years

| | | | | |
|-----------------------------------|------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 21.2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Positive Predictive Value (PPV)

| | |
|--|---|
| End point title | Maximum Positive Predictive Value (PPV) |
| End point description: | |
| Retrospective assessment of potential cytokine release syndrome (CRS) predictive models considering also data from other CTL019 trials. The Positive Predictive Value (PPV) is the percentage of participants who actually had severe CRS out of all the cases where the prediction model predicts that severe CRS will occur. The maximum PPV is the highest value attained across all potential CRS predictive models. | |
| End point type | Secondary |
| End point timeframe: | |
| Through study completion, up to 4 years | |

| | | | | |
|-----------------------------------|------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 36.0 | | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

| | |
|--|----------------------|
| End point title | All Collected Deaths |
| End point description: | |
| On-treatment deaths were collected during the pos-infusion period starting at the day of first infusion until the end of the study, up to 48 months. All deaths is the sum of pre-infusion and post-infusion deaths. | |
| Note: 33 patients were infused with tisagenlecleucel. The one death prior to infusion is an additional patient who was enrolled but not infused and is not part of the 33 infused patients. | |
| End point type | Post-hoc |
| End point timeframe: | |
| Pre-treatment deaths: from enrollment to pre-infusion; On-treatment deaths: post-infusion up to 48 months | |

| | | | | |
|---|------------------|--|--|--|
| End point values | Tisagenlecleucel | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33 | | | |
| Units: Participants | | | | |
| On-treatment deaths incl post-infusion deaths | 17 | | | |
| Deaths prior to infusion | 1 | | | |
| All Deaths | 18 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: collected during the post-infusion period, starting at the day of 1st infusion until the end of the study, up to max. duration of 48 months for each patient.

Deaths: collected at all points post-infusion until patients completed the study (LPLV).

Adverse event reporting additional description:

Any sign or symptom that occurs during the post-infusion period (starting at the day of first infusion of CTL019 until the end of the study) and safety follow-up. Deaths in the post treatment survival follow-up are not considered Adverse Events while still included in the All-Cause Mortality table.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Tisagenlecleucel - All patients |
|-----------------------|---------------------------------|

Reporting group description:

These participants were infused once with CAR-positive viable T cells.

| Serious adverse events | Tisagenlecleucel - All patients | | |
|--|---------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 33 (72.73%) | | |
| number of deaths (all causes) | 17 | | |
| number of deaths resulting from adverse events | 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Condition aggravated | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disease progression | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 33 (21.21%) | | |
| occurrences causally related to treatment / all | 4 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 8 / 33 (24.24%) | | |
| occurrences causally related to treatment / all | 8 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemophagocytic lymphohistiocytosis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Motor dysfunction | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aphasia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| 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 / 33 (6.06%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Dental caries | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proctitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Aspergillus infection | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudomonas infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Candida infection | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|---------------------------------|--|--|
| Non-serious adverse events | Tisagenlecleucel - All patients | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 33 / 33 (100.00%) | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Hypertension | | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | | |
| General disorders and administration site conditions | | | |
| Catheter site pain | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | | |
| occurrences (all) | 3 | | |
| Chills | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | | |
| occurrences (all) | 4 | | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 33 (15.15%) | | |
| occurrences (all) | 5 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Pain | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 33 (42.42%) | | |
| occurrences (all) | 25 | | |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 16 / 33 (48.48%) | | |
| occurrences (all) | 19 | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Hypogammaglobulinaemia | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | | |
| occurrences (all) | 4 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|----------------------|--|--|
| Cough subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 5 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 4 | | |
| Pleural effusion subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Tachypnoea subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Depression subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Insomnia subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 8 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 3 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 3 | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 6 | | |
| Blood lactate dehydrogenase increased | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | | |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 4 | | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 10 / 33 (30.30%) 19 | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 9 / 33 (27.27%) 9 | | |
| SARS-CoV-2 test positive subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Serum ferritin increased subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 4 | | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 8 / 33 (24.24%) 8 | | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | | |
| Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | | |
| Tachycardia subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 4 | | |
| Nervous system disorders | | | |

| | | | |
|--|------------------------|--|--|
| Depressed level of consciousness subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 3 | | |
| Headache subjects affected / exposed occurrences (all) | 8 / 33 (24.24%) 11 | | |
| Neuralgia subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 11 / 33 (33.33%) 18 | | |
| Bone marrow failure subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Coagulopathy subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Leukopenia subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 7 | | |
| Lymphopenia | | | |

| | | | |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Neutropenia | | | |
| subjects affected / exposed | 7 / 33 (21.21%) | | |
| occurrences (all) | 11 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | | |
| occurrences (all) | 4 | | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | | |
| occurrences (all) | 3 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 6 / 33 (18.18%) | | |
| occurrences (all) | 9 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | | |
| occurrences (all) | 3 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Nausea | | | |
| subjects affected / exposed | 9 / 33 (27.27%) | | |
| occurrences (all) | 13 | | |
| Small intestinal obstruction | | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p> | | | |
| <p>Stomatitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>5 / 33 (15.15%)</p> <p>6</p> | | | |
| <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>13 / 33 (39.39%)</p> <p>19</p> | | | |
| <p>Hepatobiliary disorders</p> <p>Cholelithiasis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p> | | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p> <p>Dry skin</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 33 (9.09%)</p> <p>3</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>3</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p> <p>Neck pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p> | | | |
| <p>Infections and infestations</p> | | | |

| | | | |
|--|----------------------|--|--|
| Myelitis subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 6 | | |
| Hyperphosphataemia subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 4 | | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 5 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 14 January 2020 | Update of inclusion criteria to allow patients between 18 and 25 years of age; Update inclusion criteria to allow Burkitt leukemia; Addition of a data monitoring committee for safety monitoring; Removed absolute lymphocyte count and absolute CD3+ T cell requirements from inclusion criteria |

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: