



Clinical trial results:

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

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CTL019B2101J |
|-----------------------|--------------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|---------------------------------------|-----|
| Is trial part of an agreed paediatric | Yes |
|---------------------------------------|-----|

| | |
|--|---------------------|
| investigation plan (PIP) | |
| EMA paediatric investigation plan number(s) | EMA-001654-PIP01-14 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Notes: | |

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 07 May 2018 |
| Is this the analysis of the primary completion data? | No |
| Notes: | |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 May 2018 |
| Was the trial ended prematurely? | No |
| Notes: | |

General information about the trial

Main objective of the trial:

The primary objectives of the study were:

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

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 15 March 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 62 |
| Worldwide total number of subjects | 62 |
| EEA total number of subjects | 0 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 1 |
| Children (2-11 years) | 30 |
| Adolescents (12-17 years) | 23 |
| Adults (18-64 years) | 8 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

A total dose of $\sim 1.5 \times 10^7$ to 5×10^9 ($\sim 0.3 \times 10^6$ to 1.0×10^8 /kg) T cells was infused.

| | |
|------------------|---------------|
| Arm title | CTL019 (CNS3) |
|------------------|---------------|

Arm description:

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

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

Dosage and administration details:

A total dose of $\sim 1.5 \times 10^7$ to 5×10^9 ($\sim 0.3 \times 10^6$ to 1.0×10^8 /kg) T cells was infused.

| | |
|------------------|-------------------|
| Arm title | CTL019 (lymphoma) |
|------------------|-------------------|

Arm description:

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

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

Dosage and administration details:

A total dose of $\sim 1.5 \times 10^7$ to 5×10^9 ($\sim 0.3 \times 10^6$ to $1.0 \times 10^8/\text{kg}$) T cells was infused.

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

Baseline characteristics

Reporting groups

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

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

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

End points

End points reporting groups

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

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

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

Notes:

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

Justification: No statistical analysis was planned for this endpoint

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from the infusion until week 24

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from the infusion until week 24

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from the infusion until week 24

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from the infusion until week 24

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

CAR+ cells measured by flow cytometry

End point type

Primary

End point timeframe:

from the infusion until week 24

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Peripheral blood PK parameters for % CD3+/CAR+ by flow cytometry by Day 28 disease response for Non-CNS3 ALL subjects: Cmax, Clast ^[8] |
|-----------------|---|

End point description:

CAR+ cells measured by flow cytometry

End point type

Primary

End point timeframe:

from infusion until 24 months

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

| End point values | CR/CRi | NR | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 54 | 3 | | |
| Units: Percentage | | | | |
| geometric mean (geometric coefficient of variation) | | | | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

CAR+ cells measured by flow cytometry

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

End point timeframe:

from infusion until week 24

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

CAR+ cells measured by flow cytometry

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

End point timeframe:

from infusion until week 24

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

ORR, defined as the percentage of patients with a best overall disease response of CR or CRi, was assessed in the full analysis set (FAS).

The CR rate at Day 28 was defined as the proportion of patients with an overall disease response of CR or CRi at Day 28 visit. Disease assessment performed between study Day 2 to Day 59 and prior to new therapy were considered within the window.

Flow-based clinical minimal residual disease (MRD) assessment was performed and is the percentage of patients achieving MRD negative bone marrow post-infusion and before relapse, among all patients who achieved CR or CRi.

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

End point timeframe:

from the infusion until week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from the infusion until week 24

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from the infusion until week 24

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from the infusion until week 24

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from the infusion until week 24

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

from infusion until 24 weeks

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

All subjects who received one or more tisagenlecleucel infusions

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 62 (1.61%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

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

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| 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. |
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Notes: