# Tisagenlecleucel in adult patients with aggressive B-cell non-Hodgkin lymphoma

| | | |
|---|---|---|
| **Estado** | **Tipo de Participantes** | **Rangos de Edad** |
| EC Finalizado | No aportado | Mayores de 64 , Adultos (18-64 años) |
| **Género** | **Fases** | **Participantes esperados** |
| Ambos | Fase III | 348 |
| **Resultados** | **Bajo nivel intervención** | **Enfermedad rara** |
| Sin resultados | No | No |
| **Cobertura geográfica** | **Ámbitos del ensayo** | **Terapia avanzada** |
| Multicéntrico internacional | tratamiento, seguridad, eficacia, farmacocinética, farmacodinamica, dosis | NO |

# Información

## Identificador
2023-508343-48-00 (CTIS)

## Cod. Protocolo
CCTL019H2301

Transicionado 2016-002966-29

## Área terapéutica
Enfermedades [C] - Cáncer [C04]|

## Enfermedad investigada
Adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma

## Título Científico
Tisagenlecleucel versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: A randomized, open label, phase III trial (BELINDA)

## Justificación

No aportado

## Objetivo Principal

Compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease progression (PD)/stable disease (SD) at or after the Week 12 assessment; or death at any time.

## Variables de Evaluación Primaria

EFS, defined as time from date of randomization to the date of first documented disease progression or stable disease at or after the week 12 (±1 week) assessment, as assessed by blinded independent review committee (BIRC) per Lugano criteria, or death at any time

## Momentos temporales de evaluación primaria

No aportado

## Objetivo Secundario

To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to EFS by local investigator
To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall survival (OS)
To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall response rate (ORR) and duration of response (DOR) by BIRC and local investigator.
To compare tisagenlecleucel treatment strategy and SOC treatment strategy with respect to time to response (TTR).
To evaluate safety and tolerability of tisagenlecleucel treatment strategy versus SOC treatment strategy.
To compare patient reported outcomes (PROs) of health-related quality of life (HRQoL) in both treatment arms.
Evaluate efficacy and safety of both treatment arms in histological subgroups (e.g DLBCL, not otherwise specified (NOS), FL3B, other) and molecular subgroups (e.g. germinal center B-cell (GCB), activated B-cell (ABC), other)
To assess the patients treated with tisagenlecleucel (in Arm A or after crossover) treatment strategy with respect to the following objectives: - To characterize the in vivo cellular kinetics of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid (CSF) and other tissues if available), as measured by quantitative polymerase chain reaction (qPCR) summarized by clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover. - To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) and impact on cellular kinetics, efficacy, and safety in patients receiving tisagenlecleucel therapy in arm A or after crossover
To assess the patients treated with tisagenlecleucel (in Arm A or after crossover) treatment strategy with respect to the following objectives: Assess presence of replication competent lentivirus (RCL) in patients receiving tisagenlecleucel in Arm A or after crossover

## Variables de Evaluación Secundaria

EFS as assessed by local investigator

OS: defined as the time from randomization to date of death
ORR: overall response rate as per the Lugano criteria Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 (±1w) assessment will be considered progression) or death due to aggressive B-cell NHL TTR: time from the date of randomization to the date of a patient first achieved a response of CR or PR on or after the Week 12 assessment
Type, frequency and severity of serious and non-serious adverse events and laboratory abnormalities and discontinuations due to adverse events
Time to definitive deterioration in SF-36v2, FACT-Lym, and EQ-VAS
EFS, OS and AE
Summary of qPCR detected tisagenlecleucel transgene concentrations in peripheral blood and bone marrow (and other tissue, if available), and cellular kinetic parameters from peripheral blood profile samples by time point and clinical response status
Summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel Levels of pre-existing and treatment induced immunogenicity. Cellular kinetic parameters, concentration-time profile by immunogenicity category (positive/negative), and efficacy (Month 3 response)
RCL by VSV-qPCR

## Momentos temporales de evaluación secundaria

No aportado

## Criterios de Inclusión

Signed informed consent must be obtained prior to participation in the study. Patients must be 18 years of age at the time of informed consent form (ICF) signature. Histologically confirmed (by local histopathological assessment), aggressive B-cell NHL at relapse/progression or PR after front line therapy. For patients with relapse/progression if biopsy after relapse/progression is not available or not clinically feasible to obtain a new biopsy, an archival tumor biopsy from the initial diagnosis may be submitted. For patients in PR after at least 6 cycles of first line treatment, a new biopsy must be submitted. Aggressive B-cell NHL is heretofore defined by the following list of subtypes (Swerdlow et al 2016): - DLBCL, NOS, - FL grade 3B, - Primary mediastinal large B cell lymphoma (PMBCL), - T cell rich/histiocyte rich large B cell lymphoma (T/HRBCL), - DLBCL associated with chronic inflammation, - Intravascular large B-cell lymphoma, - ALK+ large B-cell lymphoma, - B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical Hodgkin Lymphoma (HL)), - High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, - High-grade B-cell lymphoma, NOS - HHV8+ DLBCL, NOS - DLBCL transforming from follicular lymphoma - DLBCL transforming from marginal zone lymphoma - DLBCL, leg type Relapse or progression within 365 days from last dose of anti-CD20 antibody and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR). Patient is considered eligible for autologous HSCT as per local investigator assessment. Note: Intention to transplant and type of high dose chemotherapy (HDCT) regimen will be documented in the IRT system at the time of study entry Disease that is both active on PET scan (defined as Deauville score of 4 or 5) and measurable on CT scan defined as: - Nodal lesions >15 mm in the long axis, regardless of the length of the short axis, and/or - Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) >10 mm in long AND short axis Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 Adequate organ function: a. Renal function defined as: - Serum creatinine of 1.5 x upper limit of normal (ULN), OR estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m2 b. Hepatic function defined as: - Alanine Transaminase (ALT) and Aspartate Transaminase (AST) 5 × ULN - Total Bilirubin 1.5 × ULN with the exception of patients with Gilbert syndrome who may be included if their total bilirubin is 3.0 × ULN and direct bilirubin 1.5 × ULN c. Hematologic Function (regardless of transfusions) defined as: - Absolute neutrophil count (ANC) >1000/mm3 - Platelets 50,000/mm3 - Hemoglobin >8.0 g/dl Only for patients with non-historical apheresis: - Absolute lymphocyte count (ALC) >300/mm3 or - Absolute number of CD3+ T cells >150/mm3 d. Adequate pulmonary function defined as: - No or mild dyspnea ( Grade 1) - Oxygen saturation measured by pulse oximetry > 90% on room air - Forced expiratory volume in 1s (FEV1) 50% or carbon monoxide diffusion test (DLCO) 50% of predicted level Must have a

leukapheresis material of non-mobilized cells available for manufacturing

## Criterios de Exclusión

Epstein Barr Virus positive (EBV+) DLBCL, NOS, Richters transformation, and Burkitt lymphoma, and primary DLBCL of CNS. Treatment with any systemic lymphoma-directed second line anticancer therapy prior to randomization. Only steroids and local irradiation are permitted for disease control Patients with active central nervous system (CNS) involvement by disease under study are excluded, except if the CNS involvement has been effectively treated and local treatment was >4 weeks before randomization Prior allogeneic HSCT Investigational medicinal product (IMP) within the last 30 days prior to screening. Note: IMPs should not be used at any time while on study until the first progression following tisagenlecleucel infusion Presence of active hepatitis B or hepatitis C HIV positive patients Clinically significant active infection confirmed by clinical evidence, imaging, or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, etc.) Patients who, in the investigators judgment and/or according to clinical standards, have a contradiction to any study procedure or have any other medical condition that may put the patient at unacceptable risk. Any of the following cardiovascular conditions: a. Unstable angina, myocardial infarction, coronary artery bypass graft (CABG), or stroke within 6 months prior to screening, b. Left ventricle ejection fraction (LVEF) <45% as determined by echocardiogram (ECHO) or magnetic resonance angiography (MRA) or multigated acquisition (MUGA) at the screening assessment. c. New York Heart Association (NYHA) functional class III or IV (Chavey et al 2001), at screening or within the past 12 months. d. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II) and third degree AV block unless adequately controlled by pacemaker implantation. e. Resting QTcF 450 msec (male) or 460 msec (female) at screening or inability to determine the QTcF interval f. Risk factors for Torsades de Pointes (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/ symptomatic bradycardia, or any of the following: i. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome ii. Concomitant medication(s) with a Known Risk of Torsades de Pointes per crediblemeds.org that cannot be discontinued or replaced by safe alternative medication Previous or concurrent malignancy except for curatively treated non-melanoma skin cancers, in situ carcinoma (e.g. cervix, breast, bladder, prostate), and cancers in complete remission for at least 3 years and without evidence of recurrence Hypersensitivity to the excipients of tisagenlecleucel or to any other drug product as advised for administration in the study protocol (e.g. lymphodepleting agents, tocilizumab) Active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS)) and clinically significant active cerebrovascular disorders (e.g., cerebral edema, posterior reversible encephalopathy syndrome (PRES)) Pregnant or nursing (lactating) women Note: Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours before leukapheresis Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception starting from the time of informed consent form (ICF) signature and for: - at least 12 months after the tisagenlecleucel infusion and until CART cells are no longer present by qPCR on two consecutive tests for patients in Arm A or patients who crossover. - a duration according to local label and physician recommendations for patients randomized to Arm B (SOC). Furthermore, patients may need to also add barrier contraception methods if required by the local label. Highly effective contraception methods include: - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy

or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. Note: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF. In addition, participants must not donate oocytes. Sexually active males who do not use a condom during intercourse starting from the time of ICF signature and for: - at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests for patients in Arm A or patients who crossover. - a duration according to local label and physician recommendations for patients randomized to Arm B (SOC) A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, participants must not donate sperm. Prior treatment with anti-CD19 therapy, adoptive T cell therapy, or any prior gene therapy product

# Calendario

(Última actualización: 02/07/2026)

| Autorización | Inicio de Ensayo | Inclusión Primer Paciente | Interrumpido | Reiniciado |
|---|---|---|---|---|
| 18/12/2018 | 21/08/2019 | 21/08/2019 | No aportado | No aportado |

| Fin de reclutamiento | Fin prematuro (España) | Fin prematuro (Global) | Fin del ensayo en España | Fin del ensayo global |
|---|---|---|---|---|
| 08/01/2021 | No aportado | No aportado | 14/01/2026 | 03/02/2026 |

# Promotor

### Novartis Pharma AG Switzerland

**Lichtstrasse 35**

**Contact Person**

Novartis Pharma Arzneimittel GmbH

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**Monetary support: N/A**

**Tipo de promotor: Comercial**

# Ceim

### CEIm Hospital Universitario Puerta de Hierro de Majadahonda

**C/ Joaquin Rodrigo, 2 Majadahonda 28222 Madrid**

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**911917479-911917662**

# Centros

Cerrado (20/05/2026)

**HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN**

Madrid

MADRID

Servicio Hematología

Cerrado (12/05/2026)

**HOSPITAL UNIVERSITARI VALL D'HEBRON**

Barcelona

BARCELONA

Hematología

Cerrado (21/05/2026)

**HOSPITAL UNIVERSITARIO DE SALAMANCA**

Salamanca

SALAMANCA

Cerrado (08/06/2026)

**HOSPITAL UNIVERSITARIO 12 DE OCTUBRE**

Madrid

MADRID

Cerrado (21/04/2026)

**Institut Catala D'oncologia**

Hospitalet de Llobregat, L'

BARCELONA

# Medicamentos

[redacted]
-
-
INTRAVENOUS INFUSION

**Código ATC: L01XA02 - CARBOPLATINO**
**Principios Activos: N/A**

**Experimental**

[redacted]
-
-
INTRAVENOUS INFUSION

**Código ATC: L01XA03 - OXALIPLATINO**
**Principios Activos: N/A**

**Experimental**

[redacted]
-
-
INTRAVENOUS

**Código ATC: L01AA09 - BENDAMUSTINA**
**Principios Activos: N/A**

**Experimental**

[redacted]
-
-
INTRAVENOUS

**Código ATC: L01CB01 - ETOPOSIDO**
**Principios Activos: N/A**

**Experimental**

[redacted]
-
-
ORAL

**Código ATC: L04AX04 - LENALIDOMIDA**
**Principios Activos: N/A**

**Experimental**

[redacted]
-
-
ORAL

**Código ATC: H02AB02 - DEXAMETASONA**
**Principios Activos: N/A**

**Experimental**

[redacted]
-
-
ORAL

**Código ATC: L01EL01 - IBRUTINIB**
**Principios Activos: N/A**

**Experimental**

[redacted]
-
-
INTRAVENOUS

**Código ATC: L01FA01 - RITUXIMAB**
**Principios Activos: N/A**

**Experimental**

-
-
INTRAVENOUS INFUSION

**Código ATC: L01AA06 - IFOSFAMIDA**
**Principios Activos: N/A**

**Experimental**

-
-
INTRAVENOUS

**Código ATC: L01AA01 - CICLOFOSFAMIDA**
**Principios Activos: N/A**

**Experimental**

# Sin resultados

# Tisagenlecleucel in adult patients with aggressive B-cell non-Hodgkin lymphoma

| | | |
|---|---|---|
| **State** | **Type of participants** | **Age Ranges** |
| Finished CT | Not provided | Older than 64 , Adults (18-64 years) |
| **Gender** | **Phases** | **Expected Participants** |
| Both | Phase III | 348 |
| **Results** | **Low level of intervention** | **Rare disease** |
| No results | No | No |
| **Geographic coverage** | **Areas of the study** | **Advanced therapy** |
| International multicenter | treatment, safety, effectiveness, pharmacokinetics, pharmacodynamics, dose | NO |

# Information

## Identifier
2023-508343-48-00 (CTIS)

## Protocol Code
CCTL019H2301

Transitioned 2016-002966-29

## Therapeutic area
Diseases [C] - Cancer [C04]|

## Investigated Disease
Adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma

## Scientific Title
Tisagenlecleucel versus standard of care in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: A randomized, open label, phase III trial (BELINDA)

## Rationale

Not provided

## Main Objective

Compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to delaying the composite event of disease progression (PD)/stable disease (SD) at or after the Week 12 assessment; or death at any time.

## Primary Endpoints

EFS, defined as time from date of randomization to the date of first documented disease progression or stable disease at or after the week 12 (±1 week) assessment, as assessed by blinded independent review committee (BIRC) per Lugano criteria, or death at any time

## Temporary moments of secondary assessment

Not provided

## Secondary Objective

To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to EFS by local investigator
To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall survival (OS)
To compare tisagenlecleucel treatment strategy to SOC treatment strategy with respect to overall response rate (ORR) and duration of response (DOR) by BIRC and local investigator.
To compare tisagenlecleucel treatment strategy and SOC treatment strategy with respect to time to response (TTR).
To evaluate safety and tolerability of tisagenlecleucel treatment strategy versus SOC treatment strategy.
To compare patient reported outcomes (PROs) of health-related quality of life (HRQoL) in both treatment arms.
Evaluate efficacy and safety of both treatment arms in histological subgroups (e.g DLBCL, not otherwise specified (NOS), FL3B, other) and molecular subgroups (e.g. germinal center B-cell (GCB), activated B-cell (ABC), other)
To assess the patients treated with tisagenlecleucel (in Arm A or after crossover) treatment strategy with respect to the following objectives: - To characterize the in vivo cellular kinetics of tisagenlecleucel transduced cells into target tissues (blood, bone marrow, cerebral spinal fluid (CSF) and other tissues if available), as measured by quantitative polymerase chain reaction (qPCR) summarized by clinical response in patients receiving tisagenlecleucel therapy in arm A or after crossover. - To characterize the incidence and prevalence of tisagenlecleucel immunogenicity (humoral and cellular) and impact on cellular kinetics, efficacy, and safety in patients receiving tisagenlecleucel therapy in arm A or after crossover
To assess the patients treated with tisagenlecleucel (in Arm A or after crossover) treatment strategy with respect to the following objectives: Assess presence of replication competent lentivirus (RCL) in patients receiving tisagenlecleucel in Arm A or after crossover

## Secondary Endpoints

EFS as assessed by local investigator

OS: defined as the time from randomization to date of death
ORR: overall response rate as per the Lugano criteria Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 (±1w) assessment will be considered progression) or death due to aggressive B-cell NHL TTR: time from the date of randomization to the date of a patient first achieved a response of CR or PR on or after the Week 12 assessment
Type, frequency and severity of serious and non-serious adverse events and laboratory abnormalities and discontinuations due to adverse events
Time to definitive deterioration in SF-36v2, FACT-Lym, and EQ-VAS
EFS, OS and AE
Summary of qPCR detected tisagenlecleucel transgene concentrations in peripheral blood and bone marrow (and other tissue, if available), and cellular kinetic parameters from peripheral blood profile samples by time point and clinical response status
Summary of pre-existing and treatment induced immunogenicity (cellular and humoral) of tisagenlecleucel Levels of pre-existing and treatment induced immunogenicity. Cellular kinetic parameters, concentration-time profile by immunogenicity category (positive/negative), and efficacy (Month 3 response)
RCL by VSV-qPCR

## Temporary moments of secondary assessment

Not provided

## Inclusion criteria

Signed informed consent must be obtained prior to participation in the study. Patients must be 18 years of age at the time of informed consent form (ICF) signature. Histologically confirmed (by local histopathological assessment), aggressive B-cell NHL at relapse/progression or PR after front line therapy. For patients with relapse/progression if biopsy after relapse/progression is not available or not clinically feasible to obtain a new biopsy, an archival tumor biopsy from the initial diagnosis may be submitted. For patients in PR after at least 6 cycles of first line treatment, a new biopsy must be submitted. Aggressive B-cell NHL is heretofore defined by the following list of subtypes (Swerdlow et al 2016): - DLBCL, NOS, - FL grade 3B, - Primary mediastinal large B cell lymphoma (PMBCL), - T cell rich/histiocyte rich large B cell lymphoma (T/HRBCL), - DLBCL associated with chronic inflammation, - Intravascular large B-cell lymphoma, - ALK+ large B-cell lymphoma, - B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical Hodgkin Lymphoma (HL)), - High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, - High-grade B-cell lymphoma, NOS - HHV8+ DLBCL, NOS - DLBCL transforming from follicular lymphoma - DLBCL transforming from marginal zone lymphoma - DLBCL, leg type Relapse or progression within 365 days from last dose of anti-CD20 antibody and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR). Patient is considered eligible for autologous HSCT as per local investigator assessment. Note: Intention to transplant and type of high dose chemotherapy (HDCT) regimen will be documented in the IRT system at the time of study entry Disease that is both active on PET scan (defined as Deauville score of 4 or 5) and measurable on CT scan defined as: - Nodal lesions >15 mm in the long axis, regardless of the length of the short axis, and/or - Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) >10 mm in long AND short axis Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 Adequate organ function: a. Renal function defined as: - Serum creatinine of 1.5 x upper limit of normal (ULN), OR estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m2 b. Hepatic function defined as: - Alanine Transaminase (ALT) and Aspartate Transaminase (AST) 5 × ULN - Total Bilirubin 1.5 × ULN with the exception of patients with Gilbert syndrome who may be included if their total bilirubin is 3.0 × ULN and direct bilirubin 1.5 × ULN c. Hematologic Function (regardless of transfusions) defined as: - Absolute neutrophil count (ANC) >1000/mm3 - Platelets 50,000/mm3 - Hemoglobin >8.0 g/dl Only for patients with non-historical apheresis: - Absolute lymphocyte count (ALC) >300/mm3 or - Absolute number of CD3+ T cells >150/mm3 d. Adequate pulmonary function defined as: - No or mild dyspnea ( Grade 1) - Oxygen saturation measured by pulse oximetry > 90% on room air - Forced expiratory volume in 1s (FEV1) 50% or carbon monoxide diffusion test (DLCO) 50% of predicted level Must have a

leukapheresis material of non-mobilized cells available for manufacturing

## Exclusion criteria

Epstein Barr Virus positive (EBV+) DLBCL, NOS, Richters transformation, and Burkitt lymphoma, and primary DLBCL of CNS. Treatment with any systemic lymphoma-directed second line anticancer therapy prior to randomization. Only steroids and local irradiation are permitted for disease control Patients with active central nervous system (CNS) involvement by disease under study are excluded, except if the CNS involvement has been effectively treated and local treatment was >4 weeks before randomization Prior allogeneic HSCT Investigational medicinal product (IMP) within the last 30 days prior to screening. Note: IMPs should not be used at any time while on study until the first progression following tisagenlecleucel infusion Presence of active hepatitis B or hepatitis C HIV positive patients Clinically significant active infection confirmed by clinical evidence, imaging, or positive laboratory tests (e.g., blood cultures, PCR for DNA/RNA, etc.) Patients who, in the investigators judgment and/or according to clinical standards, have a contradiction to any study procedure or have any other medical condition that may put the patient at unacceptable risk. Any of the following cardiovascular conditions: a. Unstable angina, myocardial infarction, coronary artery bypass graft (CABG), or stroke within 6 months prior to screening, b. Left ventricle ejection fraction (LVEF) <45% as determined by echocardiogram (ECHO) or magnetic resonance angiography (MRA) or multigated acquisition (MUGA) at the screening assessment. c. New York Heart Association (NYHA) functional class III or IV (Chavey et al 2001), at screening or within the past 12 months. d. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II) and third degree AV block unless adequately controlled by pacemaker implantation. e. Resting QTcF 450 msec (male) or 460 msec (female) at screening or inability to determine the QTcF interval f. Risk factors for Torsades de Pointes (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/ symptomatic bradycardia, or any of the following: i. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome ii. Concomitant medication(s) with a Known Risk of Torsades de Pointes per crediblemeds.org that cannot be discontinued or replaced by safe alternative medication Previous or concurrent malignancy except for curatively treated non-melanoma skin cancers, in situ carcinoma (e.g. cervix, breast, bladder, prostate), and cancers in complete remission for at least 3 years and without evidence of recurrence Hypersensitivity to the excipients of tisagenlecleucel or to any other drug product as advised for administration in the study protocol (e.g. lymphodepleting agents, tocilizumab) Active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS)) and clinically significant active cerebrovascular disorders (e.g., cerebral edema, posterior reversible encephalopathy syndrome (PRES)) Pregnant or nursing (lactating) women Note: Women of child-bearing potential must have a negative serum pregnancy test performed within 24 hours before leukapheresis Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception starting from the time of informed consent form (ICF) signature and for: - at least 12 months after the tisagenlecleucel infusion and until CART cells are no longer present by qPCR on two consecutive tests for patients in Arm A or patients who crossover. - a duration according to local label and physician recommendations for patients randomized to Arm B (SOC). Furthermore, patients may need to also add barrier contraception methods if required by the local label. Highly effective contraception methods include: - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy

or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. Note: If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF. In addition, participants must not donate oocytes. Sexually active males who do not use a condom during intercourse starting from the time of ICF signature and for: - at least 12 months after the tisagenlecleucel infusion and until CAR T-cells are no longer present by qPCR on two consecutive tests for patients in Arm A or patients who crossover. - a duration according to local label and physician recommendations for patients randomized to Arm B (SOC) A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, participants must not donate sperm. Prior treatment with anti-CD19 therapy, adoptive T cell therapy, or any prior gene therapy product

# Calendar

(Last Update: 02/07/2026)

| Authorization | Start of Trial | First patient inclusion | Halted | Restarted |
|---|---|---|---|---|
| 18/12/2018 | 21/08/2019 | 21/08/2019 | Not aported | Not aported |

| End of recruitment | Premature end (Spain) | Premature End (Global) | Trial end (Spain) | Trial end (Global) |
|---|---|---|---|---|
| 08/01/2021 | Not aported | Not aported | 14/01/2026 | 03/02/2026 |

# Sponsor

**Novartis Pharma AG Switzerland**

**Lichtstrasse 35**

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**Monetary support: N/A**

**Sponsor type: Commercial**

# Ceim

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**C/ Joaquin Rodrigo, 2 Majadahonda 28222 Madrid**

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**911917479-911917662**

# Sites

Closed (20/05/2026)

**HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN**

Madrid

MADRID

Servicio Hematología

Closed (12/05/2026)

**HOSPITAL UNIVERSITARI VALL D'HEBRON**

Barcelona

BARCELONA

Hematología

Closed (21/05/2026)

**HOSPITAL UNIVERSITARIO DE SALAMANCA**

Salamanca

SALAMANCA

Closed (08/06/2026)

**HOSPITAL UNIVERSITARIO 12 DE OCTUBRE**

Madrid

MADRID

Closed (21/04/2026)

**Institut Catala D'oncologia**

Hospitalet de Llobregat, L'

BARCELONA

# Medication

-
-
INTRAVENOUS INFUSION

ATC code: L01XA02 - CARBOPLATINO
Active Principles: N/A

Experimental

-
-
INTRAVENOUS INFUSION

ATC code: L01XA03 - OXALIPLATINO
Active Principles: N/A

Experimental

-
-
INTRAVENOUS

ATC code: L01AA09 - BENDAMUSTINA
Active Principles: N/A

Experimental

-
-
INTRAVENOUS

ATC code: L01CB01 - ETOPOSIDO
Active Principles: N/A

Experimental

-
-
ORAL

ATC code: L04AX04 - LENALIDOMIDA
Active Principles: N/A

Experimental

-
-
ORAL

ATC code: H02AB02 - DEXAMETASONA
Active Principles: N/A

Experimental

-
-
ORAL

ATC code: L01EL01 - IBRUTINIB
Active Principles: N/A

Experimental

-
-
INTRAVENOUS

ATC code: L01FA01 - RITUXIMAB
Active Principles: N/A

Experimental

-
-
INTRAVENOUS INFUSION

**ATC code: L01AA06 - IFOSFAMIDA**
**Active Principles: N/A**

**Experimental**

-
-
INTRAVENOUS

**ATC code: L01AA01 - CICLOFOSFAMIDA**
**Active Principles: N/A**

**Experimental**

# No results