# A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7)

Published: 28-11-2017
Last updated: 16-11-2024

Primary Objective- To determine if axicabtagene ciloleucel is superior to SOC as measured by event-free survival (EFS), as determined by blinded central reviewSecondary Objectives- To evaluate the effect of axicabtagene ciloleucel compared to SOC on...

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| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Lymphomas non-Hodgkin's B-cell |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON52520

**Source**
ToetsingOnline

**Brief title**
ZUMA-7

### Condition

- Lymphomas non-Hodgkin's B-cell
- Lymphomas non-Hodgkin's B-cell

**Synonym**
Diffuse Large B Cell Lymphoma (DLBCL), lymphatic cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Kite Pharma Inc
**Source(s) of monetary or material Support:** Kite Pharma;Inc.

## Intervention

**Keyword:** Axicabtagene ciloleucel, Diffuse Large B Cell Lymphoma (DLBCL), Efficacy, Safety

## Outcome measures

### Primary outcome

Primary endpoint:

Event Free Survival (EFS): EFS is defined as the time from randomization to the earliest date of disease progression per the Lugano Classification (Cheson et al, 2014), commencement of new lymphoma therapy, or death from any cause. Subjects not meeting the criteria for these events by the analysis data cutoff date will be censored.

For the primary analysis of EFS, disease progression events and censoring times will be determined by blinded central review. Events of new therapy and death will be based on the clinical trial database.

### Secondary outcome

Key secondary endpoints (in order of hierarchical testing):

- Objective response rate

- Overall survival

Secondary endpoints:

- EFS based on investigator disease assessments

- Modified EFS based on blinded central review and on investigator disease assessments

- Progression-free survival

- Duration of response and complete response

- Incidence of adverse events and clinically significant changes in safety lab values including antibodies to axicabtagene ciloleucel

- Changes from screening to post baseline in the global health status QoL scale and the physical functioning domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30)

- Changes from screening to post baseline in the Euro-QOL, Five Dimensions, Five Levels (EQ-5D-5L) index and visual analog scale (VAS) scores

Exploratory endpoints:

For axicabtagene ciloleucel treatment arm only:

• Levels of anti CD19 chimeric antigen receptor (CAR) T cells in blood

• Levels of cytokines in serum

For both treatment arms:

• Tumor molecular and histological characteristics by levels of PD-L1 and molecular and cytogenetic subclassifications

• Changes in the work productivity and activity impairment (WPAI) from screening to post baseline

• Time to next therapy

# Study description

**Background summary**

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers originating primarily in B lymphocytes, and to a lesser extent, in T lymphocytes and natural killer cells. NHL is the most prevalent hematological malignancy and is the seventh most common new cancer among men and women, accounting for 4% of all new cancer cases and 3% of cancer-related deaths (Howlader et al, 2015).
Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for approximately 30% to 40% of all cases (Morton et al, 2006; Sehn and Gascoyne, 2015; Chaganti et al, 2016). In the past two decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of CHOP and immunotherapy. The addition of ritixumab into combination therapies for DLBCL have greatly improved patient outcomes. However, patients with chemotherapy-refractory DLBCL following treatment under the current standards of care still have a particularly dire prognosis, with no curative treatment options (Flowers 2010). Patients with r/r DLBCL especially primary refractory and early relapse within 1 year after first-line rituximab-based chemoimmunotherapy have poor prognosis even with HDT-ASCT. Because these patients are resistant to chemotherapy, they may benefit from therapies with different mechanisms of action. Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and bi-specific T-cell engagers have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumor, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies and has opened possibilities for the treatment of patients with a wide variety of cancer types including B cell malignancies expressing the CD19 antigen. CD19 is a 95 kDa transmembrane protein expressed only in the B cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B cell malignancies including all subtypes of B cell NHL, chronic lymphocytic leukemia (CLL) and non T cell acute lymphoblastic leukemia (ALL) (Blanc et al 2011) with the exception of multiple myeloma. Although there have recent advances in novel therapies for these B cell malignancies (Wang et al 2013; Byrd et al 2013; and Furman et al 2014); most patients eventually develop resistance to approved therapies. Chimeric antigen receptor (CAR) engineered + T cell therapy may circumvent mechanisms of resistance and potentially address the unmet medical

need for these patients.
Anti-CD19 CAR T cells are autologous human T cells that have been engineered to express an extracellular single-chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3* molecules arranged in tandem.
An anti-CD19 CAR vector construct has been designed, optimized and initially tested at the Surgery Branch of the National Cancer Institute (NCI) (refer to Figure 1); (Kochenderfer et al, 2009; Kochenderfer et al, 2010). The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 (Nicholson et al, 1997). A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and expansion of anti*CD19 CAR T cells (Kowolik et al, 2006). The signaling domain of the CD3* chain is essential for T-cell activation. These fragments were cloned into the murine stem cell virus-based (MSGV1) vector, utilized to genetically engineer the autologous T cells. The safety and efficacy of anti CD19 CAR T cells has been evaluated in subjects with CD19+ B cell malignancies at the NCI (Kochenderfer et al, 2012; Kochenderfer et al, 2015; Kochenderfer et al, 2017). The same anti*CD19 CAR vector construct used in the NCI protocol, and ZUMA-1 will be used in this study.
Axicabtagene ciloleucel is an engineered autologous T cell immunotherapy by which a patient*s own T cells are collected and subsequently genetically altered to recognize CD19. CD19 is expressed on the cell surface of B-cell malignancies. In ZUMA-1, which investigated the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL, axicabtagene ciloleucel significantly improved ORR ($P < 0.0001$). The ORR was 82% with a complete response (CR) rate of 54%. At the primary analysis, 44% of subjects had ongoing responses (39% in CR).
Axicabtagene ciloleucel may have an improved efficacy and tolerability in patients with less chemo-refractory disease and lower disease burden. Therefore ZUMA-7 will recruit patients with r/r DLBCL after first-line rituximab and anthracycline-based chemotherapy. Axicabtagene ciloleucel will be compared to standard of care (SOC) to determine if axicabtagene ciloleucel is superior to SOC as measured by event-free survival (EFS), as determined by blinded central review.

**Study objective**

Primary Objective
- To determine if axicabtagene ciloleucel is superior to SOC as measured by event-free survival (EFS), as determined by blinded central review

Secondary Objectives
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on objective response rate (ORR), as determined by blinded central review
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on overall survival (OS)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on

progression-free survival (PFS)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on duration of response (DOR) and duration of complete response among responding subjects, as determined by blinded central review
- To evaluate the safety of axicabtagene ciloleucel compared to SOC
- To evaluate the effect of axicabtagene ciloleucel on patient reported outcomes (PROs) and quality of life (QoL) compared to SOC

Exploratory Objectives
- Explore mechanisms of resistance to treatment with axicabtagene ciloleucel
- Evaluate mechanistic aspects and reversibility of toxicities with axicabtagene ciloleucel
- Explore molecular and histologic characteristics of the tumor microenvironment
- Evaluate impact of disease and treatment on work productivity and activity
- Estimate time to next therapy

**Study design**

This is a Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus standard of care therapy (SOC) in subjects with r/r DLBCL. Adult subjects with r/r DLBCL after first-line rituximab and anthracycline-based chemotherapy will be randomized in a 1:1 ratio to receive axicabtagene ciloleucel or SOC. Randomization will be stratified by response to first-line therapy (primary refractory, vs relapse <=6 months of first-line therapy vs relapse > 6 and <= 12 months of first line therapy) and second line age-adjusted IPI (International Prognostic Index) (0 to 1 vs. 2 to 3) as assessed at the time of screening.
For subjects randomized to the control arm of the study, SOC will consist of a protocol- defined, platinum-based salvage combination chemotherapy regimen. Subjects who respond to second-line chemotherapy (partial response (PR) or complete response (CR)) should proceed to high-dose therapy (HDT) and autologous stem cell transplant (ASCT).
An independent Data Safety Monitoring Board (DSMB) will meet every 6 months after the first subject is randomized to review safety data and will review safety and efficacy data at the time of the planned interim futility analysis. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk versus benefit. The DSMB may meet more often as needed. Refer to protocol Section
9.9 for further details. For study requirements assigned to each study arm, please refer to the schedule of assessments
(SOA) and Section 7 of protocol for details.
A study schema is drawn out and described at the end of the protocol synopsis section.

**Intervention**

- Axicabtagene ciloleucel arm
Subjects randomized to the axicabtagene ciloleucel arm of the study will receive a 3 day conditioning chemotherapy regimen consisting of fludarabine 30 mg/m2/day and cyclophosphamide 500 mg/m2/day on day -5 to day -3 followed by two rest days (day -2 and day -1).
A single infusion of axicabtagene ciloleucel administered intravenously at a target dose of 2 x 106 anti CD19 CAR T cells/kg on day 0.

- Standard of Care arm
Subjects will receive a second-line combination chemotherapy regimen (R-ICE, R DHAP, R-ESHAP, or R-GDP) as selected by the treating investigator.
Subjects responding to second-line combination chemotherapy after 2 or 3 cycles (PR or CR) should proceed to high-dose therapy (HDT) and autologous stem cell transplant (ASCT).
Peripheral stem cell collection, HDT and ASCT infusion will be per institutional or regional guidelines.

**Study burden and risks**

As outlined in the SOAs, subjects will undergo the following procedures: collection of informed consent, medical history, physical exam, bone marrow biopsy, disease staging including a baseline PET-CT scan, and blood draws for lactate dehydrogenase levels, complete blood count (CBC) and blood chemistries. Subjects will also undergo baseline echocardiogram (ECHO) and electrocardiogram (ECG) assessments and ECOG performance status. Women of child-bearing potential will undergo a urine or serum pregnancy test.

Subjects randomized to the axicabtagene ciloleucel arm will undergo leukapheresis for the collection of peripheral blood mononuclear cells necessary for axicabtagene ciloleucel manufacturing. Conditioning chemotherapy will be followed by 2 rest days, and then infusion of axicabtagene ciloleucel. Subjects will be observed in a health care facility for at least 7 days after axicabtagene ciloleucel infusion to monitor for and manage any adverse events. Blood draws for the analysis of anti-CD19 CAR T cell levels will be performed. Additional blood draws for cytokines, anti-axicabtagene ciloleucel antibodies, and replication competent retrovirus (RCR) may be performed as clinically indicated.

Subjects randomized to the SOC arm will receive investigator*s choice of second-line combination chemotherapy from the protocol defined options. Up to 3 cycles (6-9 weeks) of combination chemotherapy will be administered every 2-3 weeks. Subjects with a PR or CR to second-line therapy should proceed to HDT-ASCT. Peripheral stem cell mobilization and leukapheresis will be performed according to institutional guidelines after the 2nd or 3rd cycle of second-line therapy to obtain a minimum target of 2 x 106 CD34+ hematopoietic stem cells per kilogram. HDT-ASCT will be performed per institutional guidelines.
Routinely throughout the conduct of the study, all subjects will be asked to

report concomitant medications and adverse events, report subsequent lymphoma therapy, answer patient reported outcomes (PROs) and will have routine disease assessments as outlined in the SOAs.
Independent of the randomized treatment arm, study procedures and disease assessments will occur at the same protocol defined time points.

The patients may experience side effects after treatment. The important identified risks for axicabtagene ciloleucel are: cytokine release syndrome (CRS, which is a symptom complex associated with the use of monoclonal antibodies and adoptive cell therapies that activate lymphocytes) and adverse events that may be attributable to CRS include fever, febrile neutropenia, hypotension, acute vascular leak
syndrome, renal failure, hypoxia, and pleural effusion; neurologic events (eg, encephalopathy, somnolence, aphasia); cytopenias and infections.

Brain swelling (cerebral edema) and spinal cord swelling (spinal cord edema) are important potential risks associated with axicabtagene ciloleucel cells and brain swelling (cerebral edema) leading to death has occurred rarely in studies involving CAR T cell products, including axicabtagene ciloleucel cells. This may require aggressive treatment including placing a breathing tube for mechanical ventilation (breathing machine), administration of medications, or surgery to decrease the swelling or pressure. The exact cause of brain and spinal cord swelling in connection with treatment of CAR T cell products is not fully understood at this time.

There also risks associated with pre-treatment with chemotherapy. The patient may experience low blood counts, including a low white blood cell count which increases the risk of infection, a decrease in the number of platelets which may cause bleeding or bruising, and a decrease in the red blood cells that carry oxygen through the body (anemia). Other risks associated with chemotherapy are infection that may be life threatening, changes in the salt content of blood and there have been rare cases of strokes.

There are also non-treatment related side effects associated with other procedures that are carried out. PET-CT scans involve an exposure to radiation which carry a slight risk of developing new tumours, the patients may also experience some discomfort, anxiety, or fatigue from lying inside the scanner. The contrast dye may cause the patient to get a metallic taste in their mouth, to feel warm and rarely cause nausea or vomiting. A bone marrow biopsy and core tumour biopsy may cause discomfort, pain, bleeding or infection at the site of biopsy. Lumbar puncture can be associated with developing a headache which may be accompanied by nausea, vomiting and dizziness. While rare, lumbar puncture may also cause a herniation near the insertion site. During the insertion of an intervenous catheter, bleeding, redness or a bruise could develop and on rare occasions an infection could occur. During the leukapheresis procedure, rare complications that could occur are lowered blood pressure, bleeding or infection. During an MRI, you will lie in a small closed area inside a large

magnetic tube. Some people are scared or anxious in small places (claustrophobic)

Patients who have r/r DLBCL especially primary refractory and early relapse within 1 year after first-line rituximab-based chemoimmunotherapy have poor prognosis even with HDT-ASCT. Conditioning chemotherapy followed by infusion of axicabtagene ciloleucel has demonstrated durable responses in the majority of patients with non-Hodgkin lymphoma (NHL) including diffuse large B cell lymphoma (DLBCL). In ZUMA-1 study, which investigated the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL, axicabtagene ciloleucel significantly improved ORR ($P < 0.0001$). The ORR was 82% with a complete response (CR) rate of 54%. At the primary analysis, 44% of subjects had ongoing responses (39% in CR).

## Contacts

**Public**
Kite Pharma Inc

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US
**Scientific**
Kite Pharma Inc

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Santa Monica CA 90404
US

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

101. Histologically proven large B-cell lymphoma including the following types defined by WHO 2016
o DLBCL not otherwise specified (including ABC/GCB)
o HGBL with or without MYC and BCL2 and/or BCL6 rearrangement
o DLBCL arising from FL
o T-cell/histiocyte rich large B-cell lymphoma
o DLBCL associated with chronic inflammation
o Primary cutaneous DLBCL, leg type
o Epstein-Barr virus (EBV) + DLBCL
102. Relapsed or refractory disease after first-line chemoimmunotherapy
- Refractory disease defined as no complete remission to first-line therapy; subjects who are intolerant to first-line therapy are excluded
Progressive disease (PD) as best response to first-line therapy
Stable disease (SD) as best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP)
PR as best response after at least 6 cycles, and biopsy-proven residual disease or disease progression <= 12 months from therapy
- Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse <= 12 months of first-line therapy
103. Subjects must have received adequate first-line therapy including at a minimum:
- Anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and
- An anthracycline containing chemotherapy regimen
104. Intent to proceed to HDT and ASCT if response to second-line therapy
105. Subjects must have radiographically documented disease
106. No known history or suspicion of central nervous system (CNS) involvement by lymphoma
107. At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic cancer therapy at the time the subject provides consent
108. Age 18 years or older at the time of informed consent
109. ECOG performance status of 0 or 1
110. Adequate bone marrow, renal, hepatic, pulmonary and cardiac function defined as:
- Absolute neutrophil count (ANC) >=1000/µL
- Platelet count >= 75,000/µL
- Absolute lymphocyte count >= 100/µL
- Creatinine clearance (as estimated by Cockcroft Gault) >= 60 mL/min
- Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) <= 2.5 upper limit of normal (ULN)
- Total bilirubin <= 1.5 mg/dl, except in subjects with Gilbert*s syndrome
- Cardiac ejection fraction >= 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant

electrocardiogram (ECG) findings
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air
111. Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

## Exclusion criteria

201. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg cervix, bladder, breast) unless disease free for at least 3 years
202. History of Richter*s transformation of CLL or PMBCL
203. History of autologous or allogeneic stem cell transplant
204. Received more than one line of therapy for DLBCL
205. Prior CD19 targeted therapy
206. Treatment with systemic immunostimulatory agents (including but not limited to interferon and IL-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first dose of axicabtagene ciloleucel or SOC
207. Prior chimeric antigen receptor therapy or other genetically modified T-cell therapy, or prior randomization into ZUMA-7
208. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
209. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment.
210. Known history of infection with human immunodeficiency virus (HIV) or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive). If there is a positive history of treated hepatitis B or hepatitis C, the viral load must be undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing.
211. Active tuberculosis
212. Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted.
213. Subjects with detectable cerebrospinal fluid malignant cells or known brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases.
214. History or presence of non-malignant CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
215. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
216. History of myocardial infarction, cardiac angioplasty or stenting,

unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months of enrollment
217. Requirement for urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression
218. History of autoimmune disease, requiring systemic immunosuppression and/or systemic disease modifying agents within the last 2 years.
219. History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed.
220. History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment
221. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
222. History of severe immediate hypersensitivity reaction to tocilizumab or any of the agents used in this study
223. Treatment with a live, attenuated vaccine within 6 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study
224. Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of chemotherapy on the fetus or infant. Subjects of either sex who are not willing to practice birth control from the time of consent and at least 6 months after the last dose of axicabtagene ciloleucel or SOC chemotherapy
225. In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

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| Recruitment status: | Completed |
| Start date (anticipated): | 06-06-2018 |
| Enrollment: | 48 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Registration: | No |

# Ethics review

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| Approved WMO Date: | 28-11-2017 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 19-03-2018 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 01-05-2018 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 18-06-2018 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 31-07-2018 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den |

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| | Haag) |
| Approved WMO Date: | 23-08-2018 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 08-10-2018 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 09-11-2018 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 12-02-2019 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 06-05-2019 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 03-06-2019 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 17-01-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 20-01-2020 |

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|---|---|
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 14-05-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 02-06-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 08-06-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 17-07-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 22-09-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 05-10-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 09-11-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

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| Approved WMO Date: | 03-12-2020 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 18-03-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 11-05-2021 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 20-05-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 27-05-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 30-08-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 23-09-2022 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 09-02-2023 |
| Application type: | Amendment |

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| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 02-05-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 31-05-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 26-06-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 26-02-2024 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 25-06-2024 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2017-002261-22-NL |
| CCMO | NL62980.000.17 |