A PHASE 2, SINGLE-ARM, MULTI-COHORT, MULTI-CENTER TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF JCAR017 IN ADULT SUBJECTS WITH AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

Published: 23-03-2018
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Primary ObjectivesCohorts 1, 2, 3, 4, and 5• Determine the efficacy, defined as overall response rate (ORR), of JCAR017 in subjects with aggressive B-cell non-Hodgkin lymphomaCohort 7• Evaluate the safety of JCAR017 treatment in subjects intended to...

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

Summary

ID

NL-OMON52985

Source
ToetsingOnline

Brief title
JCAR017-BCM-001 (0451/0216)

Condition

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

Synonym
Aggressive Non-Hodgkin B-Cell Lymphoma, fast growing B-cell cancer of the lymph nodes

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: The study sponsor as listed in question B6/B7

Intervention

Keyword: B-Cell Non-Hodgkin Lymphoma, CAR-T, Phase 2

Outcome measures

Primary outcome

- Non-Hodgkin lymphoma (NHL; including secondary central nervous system [CNS] involvement): Overall Response Rate (ORR) (Cohorts 1, 2, 3, and 4): Proportion of subjects achieving a complete response (CR) or partial response (PR) based on the Lugano classification

- Relapsed/refractory (r/r) primary central nervous system lymphoma (PCNSL): ORR (Cohort 5): Proportion of subjects achieving a complete response (CR)/complete response unconfirmed (CRu) or PR based on the International Workshop to Standardize Baseline Evaluation and Response Criteria in Primary CNS Lymphoma (Abrey, 2005) - Safety in subjects intended to be treated as outpatients (Cohort 7): Type, frequency, and severity of all adverse events (AEs), including serious adverse events (SAEs) and laboratory abnormalities

Secondary outcome

Secondary

- Safety: Type, frequency, and severity of AEs, including SAEs and laboratory abnormalities

- Safety in subjects treated as outpatients: Type, frequency, and severity of

AEs, including SAEs and laboratory abnormalities

- ORR in subjects intended to be treated as outpatients Cohort 7: Proportion of subjects achieving a CR or PR based on the Lugano classification (Cheson, 2014)

- Complete response rate (CRR): Proportion of subjects achieving a CR (or CR and CRu for subjects with PCNSL) following JCAR017 infusion

- Event-free survival (EFS): Time from JCAR017 infusion to death from any cause, progressive disease (PD), or starting a new anticancer therapy, whichever occurs first

- Progression-free survival (PFS): Time from JCAR017 infusion to the first documentation of PD, or death due to any cause, whichever occurs first

- Overall survival (OS): Time from JCAR017 infusion to time of death due to any cause

- Duration of response (DOR): Time from first response to progressive disease or death from any cause, whichever occurs first

- Pharmacokinetics (PK) by qPCR: Maximum concentration (Cmax), time to peak concentration (Tmax), area under the curve (AUC), and persistence of JCAR017 in peripheral blood as assessed by qPCR

- Health Related Quality of Life (domain of interest): HRQoL using the general health/QoL, fatigue, physical and cognitive functioning subscales of the European Organisation for Research and Treatment of Cancer - Quality of Life C30 questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-Lymphoma *Additional Concerns* subscale (FACT-LymS)

Study description

Background summary

Non-Hodgkin lymphomas (NHL) comprise a heterogeneous group of malignancies. Diffuse large B-cell lymphoma is the most frequent lymphoma subtype, representing approximately 30% of all NHL. Despite overall improvement in outcomes of DLBCL, approximately one-third of patients will develop relapsed/refractory disease that remains a major cause of mortality.

CD19 as a therapeutic target
CD19 is a 95-kDa glycoprotein present on B-cells from early development until differentiation into plasma cells. It is a member of the immunoglobulin superfamily and a component of a B-cell surface signal transduction complex that positively regulates signal transduction through the B-cell receptor. CD19 is an attractive therapeutic target because it is expressed by most B-cell malignancies, including B-cell NHL (B-NHL). Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from those of the B-cell lineage.

JCAR017 Investigational Drug Product
The JCAR017 investigational drug product is a novel, CD19-targeted, genetically modified, autologous defined composition, T cell immunotherapy. Lisocabtagene maraleucel has been accepted as the generic name for JCAR017. JCAR017 is manufactured from autologous periphearl blood mononuclear cells (PBMCs) that are obtained via standard leukapheresis collection procedures. The PBMCs undergo sequential positive selection for CD8+ and CD4+ T cells where the CD4 and CD8 purified T cell populations derived from the same starting material (leukapheresis) are separated, subsequently cryopreserved, transfected with CAR and expanded through parallel processing in order to ensure the final product is infused to the subjects in a defined cell composition. The JCAR017 investigational drug product is provided as 2 individually formulated CD8+CAR+ and CD4+CAR+ T cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and administered separately by intravenous (IV) infusion.

The purpose of this Phase 2 study is to evaluate the efficacy and safety of JCAR017 in adult subjects with aggressive B-NHL.

Study objective

Primary Objectives
Cohorts 1, 2, 3, 4, and 5
• Determine the efficacy, defined as overall response rate (ORR), of JCAR017 in subjects with aggressive B-cell non-Hodgkin lymphoma
Cohort 7
• Evaluate the safety of JCAR017 treatment in subjects intended to be treated

as outpatients

Secondary Objectives
• Evaluate the safety and feasibility of administering JCAR017 (Cohorts 1, 2, 3, 4, and 5)
• To determine the efficacy, defined as ORR of JCAR017 in subjects intended to be treated as outpatients (Cohort 7)
• Evaluate other measures of efficacy of JCAR017 (eg, complete response rate [CRR], event-free survival [EFS], progression-free survival [PFS], overall survival [OS], duration of response [DOR])
• Characterize the pharmacokinetic (PK) profile of JCAR017 in the peripheral blood measured using quantitative polymerase chain reaction (qPCR) detection for the JCAR017 vector sequence
Describe changes in health-related quality of life (HRQoL) using global health/QoL, fatigue, physical and cognitive functioning subscales of the European Organisation for Research and Treatment of Cancer - Quality of Life C30 questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-Lymphoma *Additional concerns* subscale (FACT-LymS)

Study design

Study JCAR017-BCM-001 is a single-arm, multi-cohort, multi-center, Phase 2 study to determine the efficacy and safety of JCAR017 in subjects with aggressive B-cell NHL (B-NHL).
Approximately 116 subjects will be enrolled into one of 6 cohorts as listed below:
• Cohort 1: Subjects with diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS; de novo or transformed follicular lymphoma [tFL]), high-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology [HGBL]) and follicular lymphoma Grade 3B (FL3B) per World Health Organization (WHO) 2016 classification (Swerdlow, 2016), after >= 2 lines of therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
• Cohort 2: Transplant not eligible (TNE) subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification, who failed first line therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)

The first 3 subjects in Europe in Cohort 1 will be treated with a minimum interval of 14 days between JCAR017 infusions and assessed for acute safety 28 days after the third subject has received JCAR017 infusion. In addition, the product characteristics of the JCAR017 cell product manufactured with processing steps in Europe will be evaluated. If criteria for safety and feasibility are met, Cohort 1 will continue enrollment without gating and additional Cohorts 2, 4, 5 and 7 may be opened at Celgene*s discretion, A minimum of 14 days treatment interval will also apply to all subjects treated in Cohort 5.
The first 10 subjects treated with JCAR017 in Europe must be hospitalized for a

minimum of 14 days after JCAR017 infusion, unless otherwise recommended by a local authority. Experience to date with JCAR017 from the Juno TRANSCEND NHL 001 (017001) study suggests that outpatient administration of JCAR017 can be provided safely without compromising the subject*s safety when appropriate education is provided and hospital admission is done upon symptoms of toxicity. Outpatient infusion of JCAR017 was associated with a 68% decrease in hospital length of stay (Palomba, 2018). Selected countries/sites will participate in the dedicated outpatient cohort. In order to enroll subjects in Cohort 7, sites must have treated at least 3 DLBCL subjects with CD19-targeted CAR T cell therapy, and must have a suitable infrastructure to allow for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.

Safety data will be reviewed on an ongoing basis. An early safety assessment will be performed 28 days after JCAR017 is administered to the 10th subject treated in Europe. Enrollment will be halted if the observed mortality rate is > 30%, irrespective of causality, or if > 50% of subjects who undergo leukapheresis fail to have a satisfactory cell product available for infusion.

In addition, an early safety assessment will be performed 28 days after JCAR017 is administered to the 10th subject treated in Cohort 2. Enrollment into Cohort 2 will be halted if the observed mortality rate within 28 days post infusion is > 30% (excluding death related to disease progression or relapse).

The first 3 subjects in Japan will be treated with a minimum interval of 14 days between JCAR017 infusions and assessed for acute safety 28 days after the third subject has received JCAR017 infusion. In addition, the first 10 subjects treated with JCAR017 in Japan must be hospitalized for a minimum of 14 days after JCAR017 infusion. The acute and subacute toxicity profile of JCAR017 cell product manufactured entirely at the current manufacturing site in the United States (US) has already been established in subjects with relapsed/refractory (r/r) B-NHL with good tolerability observed in subjects with DLBCL (Abramson, 2018).

In addition, a staggered dosing approach will also be utilized for all new sites (Europe and Japan) without prior experience of administering CAR T cell therapies as follows:

• 1st subject infusion, wait 14 days
• 2nd subject infusion, wait 14 days

Following completion of the site-staggered enrollment approach for the first 2 subjects, the site may proceed with subject enrollment as communicated by Celgene.

Prior to initiation of any study procedure (screening period), subjects must provide informed consent. Once enrolled and during the pretreatment period, subjects will undergo leukapheresis to enable JCAR017 cell product generation. Upon successful JCAR017 cell product generation, subjects will enter the treatment period and receive lymphodepleting (LD) chemotherapy followed by infusion of JCAR017, 2 to 7 days after completion of LD chemotherapy. JCAR017 will be administered at a dose of 100 x 10^6 JCAR017-positive transfected viable T cells (CAR+ T cells).

After treatment with JCAR017, subjects will enter the post-treatment period. A

first response assessment will be performed 28 days after JCAR017 infusion. Subjects will be followed for 2 years after their JCAR017 infusion for safety, disease status, survival and health-related quality of life and utility values measured using EORTC QLQ-C30 and EQ-5D-5L questionnaires and the FACT-LymS. In addition, when feasible, all subjects will be invited to participate in interviews during their participation in the study to document their experience with JCAR017.
Delayed adverse events following exposure to gene modified T cells will be assessed and longterm persistence of these modified T cells, including vector integration sites as well as the generation of replication competent retrovirus will continue to be monitored under a separate Long-term follow-up (LTFU) protocol for up to 15 years after JCAR017 infusion as per competent authority guidelines.
The decision to discontinue a subject from the study is the responsibility of the Investigator or designee. Celgene will not delay or refuse this decision. However, prior to discontinuing a subject, the Investigator should contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

Intervention

Lymphodepleting chemotherapy followed by infusion with a JCAR017 dose of 100 x 10^6 CAR+T cells

Study burden and risks

Participation in the study will involve risks from the study procedures, from treatment with lymphodepleting chemotherapy and from treatment with JCAR017.The two most significant side effects that have been observed to occur with genetically modified T cells in previous studies are cytokine release syndrome (CRS) and neurologic toxicity.
Participation in the study also means additional time from participants (up to 22 hospital visits), additional or longer hospital stays up to 14 days, additional tests and instructions to be followed.

The available efficacy and safety findings from clinical experience with JCAR017 treated subjects reflect protocol amendments designed to assist patient selection, reduce patient risk and facilitate safety monitoring. The experience to date indicates that the benefit-risk for JCAR017 in the patient populations under study continues to remain favorable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Subjects must satisfy the following criteria to be enrolled in the study:
1. Subject is >= 18 years of age at the time of signing the informed consent form (ICF)

2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted

3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements

4. Investigator considers the subject is appropriate for adoptive T cell therapy

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Subjects not eligible for transplant (TNE) in Cohorts 2 and 3 and subjects in Cohort 5 may be enrolled with ECOG of 2 only if they meet all other inclusion/exclusion criteria.

6. Subjects with one of the following:
• Cohort 1: Subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), after >= 2 lines of therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
• Cohort 2: Transplant not eligible subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), who failed first line therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
o Transplant not eligible subjects will include those who are deemed ineligible for high-dose chemotherapy and HSCT due to age, performance status or comorbidity, while also having adequate organ function for CAR T cell treatment. At the very least, subjects have to meet one of the following criteria:
a) Age >= 70 years
b) ECOG performance status >= 2
c) Impaired pulmonary function (DLCO <= 60%, adjusted for hemoglobin concentration using the Dinakara equation)
d) Impaired cardiac function (LVEF < 50%)
e) Impaired renal function (CrCl < 60 mL/min)
f) Impaired hepatic function (AST/ALT > 2 x ULN, bilirubin >= 2 mg/dL or cirrhosis Child-Pugh B or C)
o Subjects must fulfill all other inclusion and exclusion criteria
• Cohort 3 (Japan only): Subjects meeting eligibility criteria for either Cohort 1 or 2
• Cohort 4: Subjects with newly diagnosed HGBL. Subjects must be eligible for anthracycline and rituximab (or other CD20-targeted agent) containing regimen as induction prior to consolidation with JCAR017**
• Cohort 5: Subjects with PCNSL who failed first line therapy with HDCT and ASCT, or who failed to proceed to HDCT and ASCT due to failure of PBSC mobilization or insufficient response at the completion of induction therapy with high-dose methotrexate-based polychemotherapy regimen (eg, high dose methotrexate, high dose cytarabine, rituximab and thiotepa [MATRix regimen])
• Cohort 6: (REMOVED)
• Cohort 7: Subjects meeting eligibility criteria for Cohort 1 and suitable for outpatient treatment***

* For subjects with transformed disease, the subject should have had at least 2 lines of systemic therapy for his/her transformed disease (ie, DLBCL) for Cohort 1 and 1 line for Cohort 2 to be eligible. Lines of therapy do not include those given for a previously indolent condition (ie, follicular lymphoma). Subjects do NOT have to have anthracycline for their DLBCL if received for indolent disease.

** For subjects already undergoing anthracycline and rituximab containing regimen, eligibility is to be discussed with Medical Monitor. Subjects with complete metabolic response after 2 cycles of induction will proceed with JCAR017 infusion only at time of relapse, if applicable.

*** Subjects must meet the conditions for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.

Note: Subjects with secondary CNS lymphoma involvement may enroll in Cohorts 1 to 4 and 7; subjects with PCNSL are eligible for Cohort 5. Subject selection must consider clinical risk factors for adverse events (AEs) and serious adverse events (SAEs) and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject. For Cohort 5 and to not compromise safety, subject selection has been restricted to those fit enough to be considered HDCT and ASCT as their prior therapy.

7. Histological confirmation of diagnosis at last relapse. Enough tumor material must be available for central confirmation of diagnosis, otherwise a new tumor biopsy is mandated. Note: If the subject did not experience CR since last biopsy, the most recent biopsy will be considered adequate to participate in the trial. For subjects with PCNSL, at a minimum, corresponding pathology report is required if archival tumor material is not available and repeated biopsy not feasible.

8. For subjects with NHL (except Cohort 5): Subjects must have positron emission tomography (PET)-positive disease as per Lugano Classification (Cheson, 2014)

9. For subjects with PCNSL: Subjects must have disease that is objectively measurable by International Workshop to Standardize Baseline Evaluation and Response Criteria in Primary Central Nervous System Lymphoma (Abrey, 2005). Cerebrospinal fluid (CSF). cytology will be repeated to monitor leptomeningeal disease.
Please refer to protocol section 4.2 for other inclusion criteria

Exclusion criteria

The presence of any of the following will exclude a subject from enrollment:
1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
2. Subject has any condition including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if participating in the study
3. Subject has any condition that confounds the ability to interpret data from the study
4. Subjects with T cell rich/histiocyte rich large B-cell lymphoma (THRBCL), primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma

(PMBCL), Epstein-Barr virus (EBV) positive DLBCL of the elderly, Burkitt lymphoma, and intraocular lymphoma
5. Subjects with prior history of malignancies, other than aggressive r/r NHL, unless the subject has been in remission for >= 2 years with the exception of the following noninvasive malignancies:
• Basal cell carcinoma of the skin
• Squamous cell carcinoma of the skin
• Carcinoma in situ of the cervix
• Carcinoma in situ of the breast
• Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative
• Other completely resected stage 1 solid tumor with low risk for recurrence
6. Treatment with any prior gene therapy product
7. Subjects who have received previous CD19-targeted therapy
8. Human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C:
• Subjects with a history of or active HIV are excluded
• Subjects with active hepatitis B, or active hepatitis C are excluded
• Subjects with a negative polymerase chain reaction (PCR) assay for viral load for hepatitis B or C are permitted. Subjects positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with negative viral load are eligible and should be considered for prophylactic antiviral therapy
9. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection (including tuberculosis) despite appropriate antibiotics or other treatment at the time of leukapheresis or JCAR017 infusion
10. Presence of acute or chronic graft-versus-host disease (GVHD)
11. Active autoimmune disease requiring immunosuppressive therapy
12. History of any one of the following cardiovascular conditions within the past 6 months:
• Heart failure class III or IV as defined by the New York Heart Association (NYHA)
• Cardiac angioplasty or stenting
• Myocardial infarction
• Unstable angina
• Other clinically significant cardiac disease
13. History or presence of clinically relevant CNS pathology not related to disease under study such as epilepsy, seizure, aphasia, stroke, cerebral edema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis 14. Pregnant or nursing women
15. Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis
16. Use of the following (see Section 8.2 for full details):
• Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis or 72 hours prior to JCAR017 infusion. Physiologic replacement, topical, and inhaled steroids are permitted.
• Low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide <= 300 mg/m2) given after leukapheresis to maintain disease control must be stopped >=

7 days prior to LD chemotherapy
• Cytotoxic chemotherapeutic agents that are not considered lymphotoxic within 1 week prior to leukapheresis. Oral anticancer agents, including lenalidomide and ibrutinib, are allowed if at least 3 half-lives have elapsed prior to leukapheresis
• Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide > 300 mg/m2, ifosfamide, bendamustine) within 2 weeks prior to leukapheresis
• Experimental agents within 4 weeks prior to leukapheresis unless no response or progressive disease (PD) is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
• Immunosuppressive therapies within 4 weeks prior to leukapheresis and JCAR017 infusion (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as antitumor necrosis factor [TNF], anti-IL-6, or anti-IL-6R)
• Donor lymphocyte infusions (DLI) within 6 weeks prior to JCAR017 infusion
• Radiation within 6 weeks prior to leukapheresis. Subjects must have progressive disease in irradiated lesions or have additional non-irradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional non-irradiated, measurable PETpositive lesions are present, is allowed up to 2 weeks prior to leukapheresis. Prior WBRT for subjects enrolled in Cohort 5 is not allowed
•Allogeneic HSCT within 90 days prior to leukapheresis

See protocol for additional exclusion criteria

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-11-2018
Enrollment:	6

Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	23-03-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-10-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-12-2018
Application type:	Amendment
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Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-01-2019
Application type:	Amendment
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Approved WMO Date:	07-02-2019
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Application type:	Amendment
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Approved WMO Date:	03-07-2019
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Approved WMO Date:	09-07-2019
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Approved WMO Date:	22-06-2020
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Approved WMO	

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Application type:	Amendment
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Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2023
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	EUCTR2017-000106-38-NL
ClinicalTrials.gov	NCT03484702;2017-000106-38
CCMO	NL61407.000.18