A Phase 1/2, open label, multicenter study to assess the safety and tolerability of durvalumab (anti-PD-L1 antibody) as monotherapy and in combination therapy in subjects with lymphoma or chronic lymphocytic leukemia. (MEDI4736-NHL-001). The *FUSION NHL 001* Study.

Published: 21-01-2016
Last updated: 17-04-2024

PRIMARY: Dose finding part (Phase 1):To assess the safety and tolerability of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab to determine the recommended Phase 2 doses (RP2Ds) of each...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON53056

Source
ToetsingOnline

Brief title
Celgene 0451/0182 (MEDI4736-NHL-001)

Condition

- Leukaemias
- Lymphomas non-Hodgkin's unspecified histology

Synonym
leukemia, lymph node cancer

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Celgene Coorporation

Intervention

Keyword: Chronic lymphocytic leukemia, Durvalumab, Lymphoma, Phase 1/2

Outcome measures

Primary outcome

Dose finding (Phase 1): Safety

- Non-tolerated dose (NTD), maximum-tolerated dose (MTD), and recommended Phase

2 dose (RP2D) determined based on the incidence of

DLTs that occur during the DLT evaluation period.

- Incidence of treatment-emergent adverse events using the NCI CTCAE criteria

V4.03, including dose limiting toxicities (DLTs).

Dose confirmation (Phase 1): Safety

- Incidence of treatment-emergent adverse events using the NCI CTCAE criteria

V4.03.

Dose expansion (Phase 2): Preliminary efficacy - Overall response rate (ORR)

based on the tumor specific response criteria:

- IWG Response Criteria for Malignant Lymphoma (the Lugano Classification)

ORR (lymphoma): Proportion of subjects with best response of partial response

(PR) and complete response (CR)

- IWCLL Response Criteria for CLL

ORR (CLL): Proportion of subjects with best response of CR, CR with incomplete

marrow recovery (CRi), nodular PR (nPR), PR, PR with

lymphocytosis (PRL)

Secondary outcome

Please refer to Table 2 of the protocol (version 06Nov2015) under section 2

'Study objectives and endpoints'

Study description

Background summary

Lymphoma/CLL comprise multiple histologies. It is hypothesized that durvalumab will have activity in multiple indications based on known expression pattern of PD-L1/PD-1, available preclinical data, and recent clinical data utilizing nivolumab (Ansell, 2015) or pembrolizumab (Moskowitz, 2014) in relapsed refractory classical Hodgkin lymphoma and promising early data of pidilizumab alone or in combination with rituximab (Westin, 2014) in diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL), respectively; also nivolumab monotherapy (Lesokhin, 2014) has shown antitumor activity in DLBCL, FL and T-cell lymphomas.

The programmed cell death-1 (PD-1) plays an important role in the regulation of the immune response. The PD-1 receptor, in conjunction with receptor ligands PD-L1 and PD-L2, functions to regulate the immune system primarily by down regulating signals of the T-cell receptor. PD-L1 expressed on tumor cells binds to PD-1 on T-cells which leads to down-regulation of T-cell activity and allows tumor cells to evade the immune response.

In this current trial a diverse group of lymphoma histologies (eg, R/R CLL and B-NHL) will be evaluated in both durvalumab monotherapy and durvalumab combination therapy arms in an attempt to determine dose finding/ safety, but also which lymphoma histology and treatment arms show the strongest antitumor

signals which will lead to additional clinical trials.

Study objective

PRIMARY:
Dose finding part (Phase 1):
To assess the safety and tolerability of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab to determine the recommended Phase 2 doses (RP2Ds) of each combination.

Dose confirmation part (Phase 1):
To assess the safety of durvalumab as monotherapy and when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab at the RP2D.

Dose expansion part (Phase 2):
To evaluate the preliminary efficacy of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab in subjects with lymphoma or CLL.

SECONDARY:
Dose finding and confirmation parts (Phase 1):
To make a preliminary assessment of antitumor activity of durvalumab as monotherapy and when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab in subjects with lymphoma or CLL.

Dose expansion part (Phase 2):
To assess the safety of durvalumab when given in combination with lenalidomide and rituximab; ibrutinib; or bendamustine and rituximab in subjects with lymphoma or CLL.

All parts (Phase 1/2)
To characterize the pharmacokinetics (PK) of durvalumab as monotherapy and when given in combination.
To characterize the PK of lenalidomide and ibrutinib when given in combination with durvalumab.
To determine the pharmacodynamic (Pd) effects of durvalumab as monotherapy.

EXPLORATORY:
To explore population PK analyses including the influence of intrinsic and extrinsic factors that may influence durvalumab exposures.
To determine the immunogenicity of durvalumab as monotherapy and when given in combination.
To explore PK/Pd relationship, explore pharmacodynamic mechanistic biomarkers for durvalumab and other combination agents in the study.
To explore host immune and tumor molecular markers predictive of response to durvalumab and other agents when given in combination.

To explore minimal residual disease (MRD) and its correlation with clinical outcome.
To explore the abscopal effect (ie, immune-mediated tumor response outside the radiation field) of involved field radiation therapy when given in combination with durvalumab.

Study design

This is a multicenter, open label, Phase 1/2 study assessing the safety, tolerability, PK, Pd, and preliminary efficacy of durvalumab as monotherapy and when given in combination in select subtypes of R/R lymphoma or R/R CLL.

The study will consist of 3 parts: dose finding, dose confirmation, and dose expansion. Four treatment arms will be investigated:
· Arm A (durvalumab and lenalidomide ± rituximab); discontinued to the enrollment of new subjects.
· Arm B (durvalumab and ibrutinib);
· Arm C (durvalumab and rituximab ± bendamustine); and
· Arm D (durvalumab monotherapy).

The study will start with three dose finding cohorts (Arms A, B, and C) and one dose confirmation cohort (Arm D). All 4 treatment arms will be open for enrollment at study start. Please see the figure 2 in the protocol section 3 'Overall study design' for the overall study design and table 3 for the eligible histologies.

Intervention

Study Treatments

Subjects will be assigned to 1 of the 4 treatment arms based on the investigator's choice led by the subject*s eligibility, prior antilymphoma/CLL therapy, and slot availability.

During each 28-day treatment cycle, subjects will receive durvalumab (intravenous [IV]) infusion on Day 1 of Cycles 1 through 13 at a fixed dose of 1500 mg every 4 weeks in combination with:

• Arm A: Lenalidomide orally [PO]) once daily on Days 1 to 21 (inclusive) of each cycle for 12 months (Cycles 1 through 13) in indolent lymphoma histologies (eg, follicular lymphoma [FL] or marginal zone lymphoma [MZL]) or until disease progression in aggressive lymphoma histologies (eg, diffuse large B-cell lymphoma [DLBCL]) ± rituximab (IV) infusion: Under protocol amendment 2: discontinued to the
enrollment of new subjects.

- Rituximab Schedule 1 (dose levels 2 and -1B): on Days 2, 8, 15 and 22 of Cycle 1 and on Day 1 of Cycles 2 through 5 or
- Rituximab Schedule 2 (dose levels -2 and -3): on Day 2 of Cycle 1 and on Day 1 of Cycles 2 through 8.

• Arm B: Ibrutinib (PO) continuous, once daily until disease progression.

• Arm C: Rituximab (IV) infusion on Day 2 of Cycles 1 through 6 ± bendamustine (IV) infusion on Days 1 and 2 of Cycles 1 through 6. Bendamustine may be stopped after 4 cycles if the subject experiences a cumulative toxicity related to bendamustine and there is no clinical evidence of a favorable benefit to risk ratio for continuation of bendamustine treatment per the investigator*s medical judgment.

• Arm D: Durvalumab monotherapy arm. At the time of disease progression, the investigator may add study treatments previously investigated with durvalumab in this protocol (ie, lenalidomide ± rituximab; bendamustine ± rituximab; rituximab; or ibrutinib) once a tolerable dose level is confirmed for that combination, or subjects can receive involved-field radiation to a single involved nodal site (ie, to evaluate for a systemic abscopal antitumor effect) if they meet the criteria defined in Section 3.1.2. of the protocol. Prior to addition of another therapy to durvalumab, the investigator must consult with the sponsor*s medical monitor.

Study burden and risks

The safety profile of MEDI4736 summarizes in the context of AESIs that may impact the risk-benefit balance of MEDI4736. The probability of these events occurring with MEDI4736 use continue to be characterized based on the overall strenght of evidence, from greatest to least, clinical data, nonclinical data, and pharmacologic class effects/mechanism of action. Clinically significant risks of interest include immune-mediated reactions and their associated signs and symptoms, risks due to immunogenicity and other potential risks.

See more information in section E9.

Contacts

Public
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Scientific
Celgene Corporation

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

ALL TREATMENT ARMS
1. Subject is >= 18 years of age and <= 80 years of age at the time of signing the ICF. Subjects > 80 years of age may be included if they meet criteria defined in the protocol.
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. Subject has histologically confirmed and documented eligible histologies as defined in the protocol.
5. Subject has been previously treated with at least one prior systemic chemotherapy, immunotherapy, or chemoimmunotherapy.
6. Subject with high-risk CLL/SLL is defined by the presence of at least one of the following factors:
a. Complex karyotype;
b. del (17p) abnormality;
c. Mutated TP53;
d. Ibrutinib-or other BTK-inhibitor failure or an inadequate tumor response which is less than partial response;
e. Relapsed/progressive disease within 6 months of completing their last therapy which may include investigational drug.

7. Subject is willing and able to undergo biopsy:
a. Subject with lymphoma is willing and able to undergo tumor/lymph node biopsy (incisional/excisional or multiple core needle):
- During the Screening Period
- Any time during Cycle 2 (strongly recommended), and
- At the time of disease progression from subjects who have achieved objective response (CR/PR) to study treatment.
b. Subject with CLL is willing and able to undergo bone marrow biopsy during the Screening and Treatment Periods.
Material from a fine needle aspiration is not acceptable.
8. Subject who has documented active relapsed or refractory disease requiring therapeutic intervention.
9. Subject who has measurable disease:
a. For subject with lymphoma, bi-dimensionally measurable disease on cross-sectional imaging by computed tomography (CT) with at least one nodal or extranodal lesion >=2.0 cm in its longest dimension.
Note: A previously irradiated lesion is ineligible to be used as a measurable target
lesion.
b. For subject with CLL, in need of treatment as defined by IWCLL Guidelines for the Diagnosis and Treatment of CLL (Appendix I of protocol).
Subject who has performance status of 0, 1, or 2 on the ECOG scale.
10. Subject who has life expectancy of greater than 6 months.
11. Subject who fulfills the laboratory requirements outlined in Table 6 of the protocol.
12. Female subject of childbearing potential (FCBP1) who is sexually active with a male must:
a. Have 2 negative pregnancy tests as verified by the investigator prior to starting any IP therapy. They must agree to ongoing pregnancy testing during the course of the study, and after the last dose of any IP. This applies even if the subject practices true abstinence from heterosexual contact.
b. Use effective methods (1 highly effective and 1 additional effective [barrier] method) of contraception from 28 days prior to starting durvalumab, and must agree to continue using such precautions while taking durvalumab (including dose interruptions) and for 90 days after
the last dose of durvalumab. Cessation of contraception after this point should be discussed with a responsible physician.
The following are examples of highly effective and additional effective methods of contraception:
Highly effective methods (defined as one that results in a low failure rate rate [ie, less than 1% per year] when used consistently and correctly):
(i) Intrauterine device (IUD). See Protocol Section 8.2
(ii) Hormonal (birth control pills, injections, implants). See protocol for additional information
(iii) Tubal ligation
(iv) Partner's vasectomy
Additional effective methods:

(i) Male condom
(ii) Diaphragm
(iii) Cervical cap
Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding.
Prophylactic antibiotics should be considered particularly in subjects with neutropenia.
c. Agree to abstain from breastfeeding during study participation and for at least 90 days after the last dose of durvalumab.
d. Refrain from egg cell donation while taking durvalumab and for at least 90 days after the last dose of durvalumab.
13. Male subject who is sexually active with a female partner of childbearing potential must:
a. Use male condom plus spermicide (even if he has undergone a successful vasectomy)from starting dose of durvalumab (Cycle 1 Day 1) through 90 days after receipt of the last dose of durvalumab. True abstinence is acceptable only when this is in line with the preferred and
usual lifestyle of nonsterilized male subject.
b. Refrain from semen or sperm donation while taking durvalumab and for at least 90 days after the last dose of durvalumab., See protocol for inclusion criteria specific to Arms A, B and C.

Exclusion criteria

ALL TREATMENT ARMS
1. Subject who has known or suspected central nervous system (CNS) or meningeal involvement by lymphoma.
2. Subject who has other lymphoma histologies which are not listed on Table 3, Table 4, or Table 5 of the protocol.
a. Subject who has blastoid variants of MCL or MCL with blastoid transformation.
b. Dose Confirmation and/or Expansion Parts only:
- Transformed lymphoma or Richter's transformation
- DLBCL histology other than: not otherwise specified or T-cell/histiocyte rich.
3. Subject who has any histopathologic finding consistent with myelodysplastic syndrome on bone marrow studies.
4. Subject who has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
5. Subject who has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
6. Subject who has any condition that confounds the ability to interpret data from the study.
7. Subject who has any uncontrolled inter-current illness as defined in the

protocol.
8. Subject who is concurrently enrolled in another clinical study, unless in a follow-up period or it is an observational study.
9. Subject who has any concurrently chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment.
10. Subject who has received:
a) Any systemic antilymphoma/leukemia therapy, or hematopoietic growth factors, blood or platelets transfusions within 14 days prior to the first dose of IP (ie, Cycle1 Day 1) and/or
b) Any radioimmunotherapy within 3 months prior to the first dose of IP (ie, Cycle 1
Day 1).
11. Subject who has unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 <= Grade 1 with the exception of alopecia and laboratory values listed per the exclusion criteria. Subjects with irreversible toxicity that is not reasonably
expected to be exacerbated by durvalumab or other investigational treatments may be included (eg, hearing loss) after consultation with the sponsor's medical monitor.
12. Subject who received any prior mAb against PD-1 or PD-L1 and/or any prior:
a. Arm A only: IMiDs (eg, lenalidomide, thalidomide);
b. Arm B only: ibrutinib or other BTK inhibitor;
c. Arms C only: bendamustine.
13. Subject who has history of organ transplant or allogeneic hematopoietic stem cell transplantation.
14. Subject who has taken corticosteroids during the last 1 week prior to fist dose of IP (ie,Cycle 1 Day 1), unless administered at a dose equivalent to <= 10 mg/day prednisone. See protocol for exceptions.
15. Subject who has received live, attenuated vaccine within 30 days prior to the first dose of durvalumab (NOTE: Subjects, if enrolled, should not receive live vaccine during the study and for 12 monhts after last dose of rituximab or until recovery of B-cells and for 120 days after the last dose of durvalumab, whichever is longer).
16. Subject who has undergone major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of the IP or still
recovering from prior surgery.
17. Subject who has active documented autoimmune disease prior to first dose of durvalumab.
18. Subject who has history of primary immunodeficiency or tuberculosis.
19. Subject who has known seropositivity for or active infection for human immunodeficiency virus or hepatitis C virus.
20. Subject who is seropositive for or active viral infection with hepatitis B virus (HBV)
a. HBV surface antigen (HBsAg) positive.
b. HBV surface antigen (HBsAg) negative, HBV core antibody (anti-HBc) positive, and detectable viral DNA.
21. Female subject who is pregnant, breastfeeding, or intend to become pregnant

during the participation in the study.
22. Subject who has other invasive malignancy within 2 years prior to signing the ICF except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin, ductal carcinoma in situ of the breast, or incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) that has/have been surgically cured. a. Arm A only: Subject who has history of other malignancies, unless the subject
has been free of the disease for >= 5 years prior to signing the ICF.
Exceptions: History of previously treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin and related localized non melanoma skin cancer, carcinoma in situ of the cervix, carcinoma in situ of breast, incidental histologic finding of prostate cancer (T1a or T1b
using the TNM clinical staging system).
23. Subject who has known allergy or hypersensitivity to the active substance or any of the excipients, or to other humanized mAbs., See protocol for exclusion crteria specific to Arms A, B and C.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-01-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bendamustine
Generic name:	Levact 2.5 mg/ml powder for concentrate for solution for infusion
Product type:	Medicine
Brand name:	Durvalumab
Generic name:	NA
Product type:	Medicine
Brand name:	Ibrutinib
Generic name:	IMBRUVICA 140 mg hard capsules
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lenalidomide
Generic name:	Revlimid 15 mg hard capsules
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Lenalidomide
Generic name:	Revlimid 20 mg hard capsules
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-01-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2016

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	28-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-03-2018
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	05-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

(Rotterdam)

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	EUCTR2015-003516-21-NL
CCMO	NL55850.078.16

Study results

Results posted: 09-11-2023

First publication
01-01-1900