A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma

Published: 31-05-2013
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Primary Objectives - To compare Overall Survival (OS) and Progression free survival (PFS) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53096

Source
ToetsingOnline

Brief title
Nivolumab or Nivolumab/Ipilimumab vs Ipilimumab in advanced melanoma

Condition

- Skin neoplasms malignant and unspecified

Synonym
Advanced (unresectable or metastatic) melanoma

Research involving

Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Advanced Melanoma, Ipilimumab, Nivolumab

Outcome measures

Primary outcome

The primary objective will be measured by the co-primary endpoints of overall surival (OS) and Progression Free Survival (PFS) in all randomized subjects.

OS is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive. OS data will be collected continuously while subjects are on study medication and every 3 months via in-person or phone contact after discontinuation of study medication.

PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Subjects who started anti-cancer therapy without a prior reported progression

will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy. Tumor assessments are scheduled to be performed at Week 12, every 6 Weeks up to Week 49 and then every 12 to 24 Weeks until disease progression.

Secondary outcome

The first secondary objective (to compare ORR between the experimental arms and the control group) will be measured by the endpoint of ORR. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Tumor assessments are scheduled to be performed at Week 12, every 6 Weeks up to Week 49 and then every 12 to 24 Weeks until disease progression. The second secondary objective (to evaluate differences in OS, PFS, and ORR between the two experimental arms) and will be measured by the endpoints of OS, PFS, and ORR. The third secondary objective (to evaluate PD-L1 expression as a predictive biomarker) will be measured by the endpoint OS based on PD-L1 expression level. PD-L1 expression will be evaluated in tumor specimens collected prior to randomization. The forth secondary objective (to evaluate HRQoL) will be measured by mean changes from baseline in the EORTC-QLQ-C30 global health status/QoL composite scale and by mean changes from baseline in

the remaining EORTC QLQ-C30 scales. HRQoL will be evaluated per Section 5.1 of

the protocol.

Study description

Background summary

The lifetime risk of developing invasive melanoma has been dramatically increasing and the overall mortality from melanoma continues to rise. Although in 2011, two new agents, ipilimumab and vemurafenib, were approved for advanced melanoma there is still a large unmet need for patients with previously untreated,unresectable or metastatic melanoma.
Approximately 50% of cutaneous melanoma is BRAF mutation positive, and vemurafenib is indicated for the treatment of BRAF V600E mutation positive advanced melanoma. Vemurafenib is a potent inhibitor of mutation positive BRAF and has demonstrated an increased overall survival benefit compared to dacarbazine with a hazard ratio for death of 0.62 with a median overall survival of 13.2 months versus 9.6 months for vemurafenib and dacarbazine, respectively. Besides these two agents, no other agent has demonstrated an overall survival benefit in a Phase 3 randomized study.

Ipilimumab at 3 mg/kg was chosen as the comparator because it is the only FDA approved treatment of previously untreated, unresectable or metastatic melanoma without restriction to BRAF status that has demonstrated overall survival benefit in a Phase 3 randomized trial (Ipilimumab monotherapy at 3 mg/kg has been shown to increase 2-year survival compared to a vaccine control (26% vs. 14%) in previously treated subjects with metastatic melanoma). In a retrospective analysis of a Phase 2 ipilimumab clinical trial in unresectable and metastatic melanoma, CA184004, rates of objective responses and stable disease in patients with BRAF-V600E mutation positive tumors were comparable to those in patients with the wildtype gene. Given 3 mg/kg of ipilimumab has not been evaluated in a phase 3 trial of previously untreated, unresectable or metastatic melanoma, the median overall survival has been estimated to be 14 months (as calculated in section 1.4.4.2 of the protocol - page 23).
Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced prior treated melanoma, with objective response rates of 20 - 41% in 106 melanoma subjects treated at various dose levels in CA209003. Nivolumab has also demonstrated a manageable safety profile. The most common AEs included fatigue, rash, pruritis, diarrhea, and nausea.
The combination of nivolumab and ipilimumab has the potential for increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. Preliminary analysis of the evaluable CA209004 subjects revealed that approximately 33% of the subjects had >80% tumor reductions in target lesions

by week 12. This compares favorably to < 2% for 3 mg/kg ipilimumab monotherapy based on the CA184020 (N=540) and <3% for nivolumab monotherapy based on the CA209003. However, the combination of nivolumab and ipilimumab also has the potential for increased frequencies of adverse events. The most common (reported at > 10% incidence) treatment related AEs are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased and vitiligo. Although the preliminary data suggests an increase in adverse event frequency of nivolumab combined with ipilimumab compared to ipilimumab monotherapy or nivolumab monotherapy, there were no unexpected adverse events noted in the combination of nivolumab and ipilimumab. In addition, many of the Grade 3-4 adverse events associated with the nivolumab combined with ipilimumab were laboratory in nature, without clinical sequalae and adverse events have been manageable and reversible following intervention dose delays or with systemic steroid treatment. Evaluating both nivolumab monotherapy and the combination of nivolumab and ipilimumab will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on the individual risk-benefit ratio. The robust clinical activity demonstrated by nivolumab monotherapy and the promising clinical activity of nivolumab combined with ipilimumab in subjects with advanced melanoma in combination with the manageable safety profile and the lack of approved survival-prolonging agents for a large segment of the previously untreated population supports the further development of nivolumab and nivolumab combined with ipilimumab in subjects with previously untreated, unresectable or metastatic melanoma.

Study objective

Primary Objectives -
To compare Overall Survival (OS) and Progression free survival (PFS) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma.
Secondary Objectives -
To compare ORR of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate differences in OS, PFS, and ORR between nivolumab combined with ipilimumab and nivolumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate whether PD-L1 expression is a predictive biomarker for PFS and OS
- To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organisation for Research and Treatment of Care (EORTC) QLQ-C30
Exploratory Objectives - To evaluate duration of and time to objective response of nivolumab monotherapy, nivolumab combined with ipilimumab, and ipilimumab in subjects with unresectable or metastatic melanoma - To assess the overall safety and tolerability of nivolumab monotherapy, nivolumab combined with

ipilimumab, and ipilimumab monotherapy in subjects with unresectable or advanced melanoma - To characterize pharmacokinetics of nivolumab and ipilimumab administered alone or in combination with nivolumab - To characterize the immunogenicity of nivolumab and nivolumab combined with ipilimumab - To evaluate pharmacokinetic drug-drug interaction between nivolumab and ipilimumab - To explore potential biomarkers associated with clinical efficacy (ORR, PFS and OS) of nivolumab and/or nivolumab combined with ipilimumab by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, PBMCs) in comparison to clinical outcomes. - To assess the effects of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4 on clinical endpoints and/or on the incidence of adverse events - To assess changes in health status and work and activity impairment in treatment groups using the EuroQoL EQ-5D and the Work Productivity and Activity Impairment questionnaire (WPAI-GH) respectively - To describe the quality of survival in patients after treatment discontinuation using the EuroQoL EQ-5D .

Study design

This is a Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in adult (less than or equal to 18 years) subjects with previously untreated unresectable or metastatic melanoma. Subjects must have stage III (unresectable) or stage IV melanoma, as per the American Joint Committee on Cancer (AJCC) staging system, and must not have received prior therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy is allowed in the setting of completely resectable disease. PD-L1 status will be obtained by immunohistochemical (IHC) staining of PD-L1 protein prior to randomization. Subjects will be randomized 1:1:1 and stratified by PD-L1 status (positive vs.negative/indeterminate), BRAF Status (BRAF mutation positive, BRAF wildtype), and AJCC M stage (M0/M1a/M1b vs. M1c). One cycle of treatment is defined as six weeks. Subjects will be treated with one of the following:
- Arm A: nivolumab 3 mg/kg IV every 2 weeks + ipilimumab-placebo on weeks 1, 4 and nivolumab-placebo on weeks 4 for cycles 1 and 2
- Arm B: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV every 3 weeks for 4 doses then nivolumab 3 mg/kg IV Q2W + nivolumab-placebo on weeks 3 and 5 for cycles 1 and 2.
- Arm C: ipilimumab 3mg/kg IV every 3 weeks for a total of 4 doses + nivolumab-placebo on weeks 1, 3, 4 and 5 for cycles 1 and 2 then every 2 weeks.
This study will consist of 3 phases: screening (up to 28 days), treatment and follow-up. Treatment will continue until documented disease progression, there is discontinuation due to toxicity, withdrawal of consent or the study ends. Subjects will be followed every 3 months for survival after completion of the follow-up visits. Subjects in Arm C who were receiving nivolumab - placebo will enter the follow-up phase upon unblinding of the study.

Intervention

The medical interventions for this trial include both Nivolumab and Ipilimumab.
All compounds will be supplied by the Sponsor company.
One cycle of treatment is defined as six weeks. Subjects will be treated with one of the following:
- Arm A: nivolumab 3 mg/kg IV every 2 weeks + ipilimumab-placebo on weeks 1, 4 and nivolumab-placebo on weeks 4 for cycles 1 and 2
- Arm B: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV every 3 weeks for 4 doses then nivolumab 3 mg/kg IV Q2W + nivolumab-placebo on weeks 3 and 5 for cycles 1 and 2.
- Arm C: ipilimumab 3mg/kg IV every 3 weeks for a total of 4 doses + nivolumab-placebo on weeks 1, 3, 4 and 5 for cycles 1 and 2 then every 2 weeks.
Beyond the first 2 cycles (12 weeks), subjects will be receiving infusions (Nivolumab for arm A and B and Nivolumab macthing placebo for arm C) every 2 weeks for 60 minites.
Subjects in Arm C who were receiving nivolumab - placebo will enter the follow-up phase upon unblinding of the study.

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinationd, vital sign measurements including oxygen saturation levels, blood tests for safety assessment, pregnancy testing (for females of child bearing potential) and monitoring for adverse events. In addition, every 6 weeks (from week 12 up until the 1st year), patients will undergo radiographic assessment of their tumours (by CT or MRI) until disease progression of treatment discontinuation whichever occurs later. Beyond year one, the radiographic assessment of their tumours (by CT or MRI) will be every 12 to 24 weeks. Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. There procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient. Treatment for cancer often has side effects, including some that are lift threatening. An independent Data Monitoring Committee (DMC) will be utilised in this trial.

Contacts

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed Written Informed Consent
a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care
b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study
2. Target Population
a) Histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system.
b) Eastern Cooperative Oncology Group (ECOG) performance status of * 1 (Refer to Appendix 2)
c) Treatment naïve subjects (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma). Note that prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to randomization, and all related adverse events have either returned to baseline or stabilized.
d) Measurable disease by CT or MRI per RECIST 1.1 criteria.5.4.3.1
e) Tumor tissue from an unresectable or metastatic site of disease must be

provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses.
f) Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period
g) Prior radiotherapy must have been completed at least 2 weeks prior to study drug administration.

Screening laboratory values must meet the following criteria and should be obtained
within 14 days prior to randomization:
- WBC greater than or equal to 2000/µL
- Neutrophils greater than or equal to 1500/µL
- Platelets greater than or equal to 100 x103/µL
- Hemoglobin > 9.0 g/dL
- Serum creatinine less than or equal to 1.5 x ULN or creatinine clearance (CrCl) greater than or equal to 40 mL/min (using the Cockcroft-Gault formula):
- AST/ALT less tha or equal to 3 x ULN
- Total Bilirubin less than or equal to 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).
i) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated) after obtaining agreement from the medical monitor prior to re enrolling a subject. If re-enrolled, the subject must be re-consented.
3. Age and Reproductive Status
a) Men and women, less than or equal to 18 years of age
b) Women of childbearing potential (WOCBP) must use method(s) of contraception as indicated in Appendix 5. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception and duration should be determined in consultation with the investigator. WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 30 days plus the time required for the investigational drug to undergo five half lives. The half life of BMS- 936558 and ipilimumab is up to 25 days and 18 days, respectively. Given the blinded nature of this study, WOCBP should therefore use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half lives) after the last dose of investigational drug.
c) Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

d) Women must not be breastfeeding
e) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year The investigator shall review contraception methods and the time period that contraception must be followed. Men that are sexually active with WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 90 days plus the time required for the investigational drug to undergo five half lives. The half-life of nivolumab and ipilimumab is up to 25 days and 18 days, respectively. Given the blinded nature of the study, men who are sexually active with WOCBP must continue contraception for 31 weeks (90 days plus the time required for nivolumab to undergo five half lives) after the last dose of investigational drug.
f) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile; see Section 3.3.3 for the definition of WOCBP) and azoospermic men do not require contraception.

Exclusion criteria

1. Target Disease Exceptions
a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
b) Ocular melanoma
2. Medical History and Concurrent Diseases
a) Any participation in a Phase 3 ipilimumab trial
b) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.
c) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
d) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
e) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other

immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
f) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
3. Physical and Laboratory Test Findings
a) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection
b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
4. Allergies and Adverse Drug Reaction
a) History of allergy to study drug components.
b) History of severe hypersensitivity reaction to any monoclonal antibody.

5. Sex and Reproductive Status
a) WOCBP who are pregnant or breastfeeding
b) Women with a positive pregnancy test at enrollment or prior to administration of study medication.
6. Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	16-09-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ipilimumab
Generic name:	Ipilimumab
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	Nivolumab

Ethics review

Approved WMO Date:	31-05-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-11-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	25-11-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-06-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-09-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-12-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	20-01-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-02-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-03-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-06-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	10-07-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	30-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	28-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2022
Application type:	Amendment
Review commission:	METC NedMec
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Date:	27-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2012-005371-13-NL
ClinicalTrials.gov	NCT01844505
CCMO	NL44310.031.13