Neoadjuvant immune checkpoint inhibition and novel IO combinations in early-stage colon cancer. The NICHE trial.

Published: 19-09-2016
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This study has been transitioned to CTIS with ID 2024-513314-35-00 check the CTIS register for the current data. Primary Objective: To determine the safety and feasibility of pre-operative immunotherapy in CRC. Additional Primary Objective for the...

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

Summary

ID

NL-OMON53138

Source
ToetsingOnline

Brief title
Neoadjuvant Immunotherapy in early stage colon cancers (NICHE)

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
colon carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Bristol-Myers Squibb,medicatie via BMS

Intervention

Keyword: colon, ipilimumab, neoadjuvant, nivolumab

Outcome measures

Primary outcome

Primary endpoint for the MSS and MSI cohort: safety and feasibility, as measured by time to surgery within the predefined 6 weeks. Unacceptable treatment-related complications is defined as those leading to delays in surgery of more than 2 weeks in >15%of patients. Even though 15% is high, we would accept a higher rate of delays since the treatment is effective in 100% of patients so far and there seems to be no risk of progressive disease by delaying surgery. We expect >95% of patients to undergo surgery without delays of more than 2 weeks past the predefined 6 weeks within the study protocol. Delays due to logistical reasons, pandemics or other serious adverse events which are not treatment related will not be considered as treatment-related complications.

Additional Primary endpoint for the expanded MSI cohort: 3-year disease-free survival. A two-sided, one-sample logrank test calculated for a sample of 100 patients has 80% power at a 0.025 significance level (split alpha due to two primary endpoints) to detect a 3-year DFS of 93% if the 3-year DFS in the historic control group is (or synthetic matched control group) is 82%.

Secondary outcome

Secondary endpoints:

- To assess the major pathological response rate (MPR, <10% viable tumor rest)

and complete response rate and whether response correlates with DFS;

- To find biomarkers and evaluation strategies able to accurately assess complete and near-complete responses in order to pursue organ-sparing treatment (omission of surgery) in this patient population in future trials:

o Post-treatment CT-scans: can we use radiomics to accurately assess complete and near-complete response?

o ctDNA analysis: can we use ctDNA to assess complete response and is there a difference between complete and near-complete response in terms of minimal residual disease on ctDNA and risk of relapse?

- To expand current exploratory translational analyses, in terms of;

o RNA sequencing and inflammatory signatures to find signatures predictive of response and possible escape mechanisms in non-responding tumors;

- Analysis of immune cell infiltration and the difference with inflamed pMMR tumors pre- and post-treatment: why is there no pathological response in pMMR tumors showing immune activation? And are there any differences between complete and near-complete responders?

- To assess the efficacy of nivolumab plus anti-IL8 and the predictive value of serum IL-8 in terms of pathological response

- Primary readout will be the effect of therapy on intratumoral T-cell infiltration, CD4, CD8 infiltration and immune checkpoints upregulation in the time interval pre- and post-treatment in biopsies.

- Immunogenic mutational load will be determined by tumor tissue DNA WES. Peripheral blood DNA WES will also be performed and used as a control for somatic mutation sorting (only genes relating to colon cancer and/or

immune-related genes, deemed informational for this study, will be assessed).

- Immune suppressive pathways, IFN-y induced gene expression and COX2 induced gene expression changes will be analyzed by use of RNA sequencing on pre- and post-therapy tissue;

- Date of relapse, as determined by disease recurrence or disease-related death during follow-up after surgery. Follow-up will be performed according to local and/or national guidelines;

- Association between microbiota composition and treatment outcomes and the effect of neoadjuvant nivolumab plus ipilimumab on the gut microbiota composition

- Fresh tissue for the generation of organoids or the use for other analyses using tumor digest, will be collected whenever possible.

Study description

Background summary

Currently, it is not standard of care to give pre-operative treatment is to patients with colon cancer. However, based on the FOXTROT data national guidelines for the treatment of colon cancer will advise consideration of neoadjuvant chemotherapy when a T4 tumor is suspected. There are no specific advices with regards to MSI or MSS tumors yet, awaiting the next update of these guidelines and incorporation of the FOXTROT data for MSI tumors after publication (considering the lack of pathological response in most patients with MSI tumors). Post-operative adjuvant chemotherapy is commonly administered to patients with stage 3 tumors and in high risk stage 2 tumors (only MSS), and has been shown to marginally increase PFS and OS, the latter by approximately 5%.

Patients within the NICHE trial are exposed to immunotherapeutic drugs, which may lead to immune related adverse events. We expect the limited exposure to these drugs within this study to carry a low risk of adverse events and no significant delays in surgical resection of the primary tumor. The first

results of the NICHE trial have recently been published, showing that this treatment is safe and feasible, without any delays in surgery and without any unexpected toxicities. As anticipated, immune-related adverse events were limited and comparable to data from studies with monotherapy PD-1 blockade, namely 13% (n=5) grade 3-4 adverse events, of which n=3 were asymptomatic increases in lipase and amylase, which resolved without intervention. Furthermore, surgical interventions in patients on immunotherapeutic regimens does not seem to increase the risk of complications, albeit with wide confidence intervals. The benefit of this treatment in MSI tumors in terms of pathological response was recently published by Chalabi M. et al, Nature Medicine, 2020, with 100% pathological response rate. Furthermore, a 27% response rate was seen in MSS tumors.

Previous reports of clinical studies using combinations of ipilimumab and nivolumab show grade 3-4 adverse events in 44-58% of patients, with 37% of treatments-related events leading to discontinuation of treatment. More recent data from the Checkmate-142 trial using the combination of nivo 3mg/kg and low dose ipilimumab (1mg/kg) every three weeks (Morse, Overman et al, The Oncologist 2019), showed 56% grade 1-2 and 24% grade 3-4 immune-related adverse events. In total, 25%, 23%, 19%, 5%, 5% and 29% experienced an endocrine, gastrointestinal, hepatic, pulmonary, renal, or skin irAE, respectively.
These findings show a favorable toxicity profile for the alternatively dosed combination of nivolumab and ipilimumab, with a low frequency of grade 3 and 4 treatment related events. Also, considering the fact that patients in this study will only receive one single low dose of ipilimumab and two cycles of nivolumab, the incidence of treatment related events seems lower than above mentioned in the first 40 patients included in the NICHE trial.

Rationale for nivolumab plus anti-IL8
The next cohort within this adaptive design will include treatment of patients with nivolumab plus anti-interleukin 8 (IL-8). In cancer, serum IL-8, released by tumor cells, has been shown to promote tumor immune evasion by recruitment of immunosuppressive neutrophils and myeloid-derived suppressor cells to the TME, which in turn could contribute to immune resistance by dampening the cytotoxic ability of T cells.
Additionally, IL-8 may promote angiogenesis and epithelial to mesenchymal transition, increasing metastatic potential and resistance to therapy. Serum IL-8 together with tumor neutrophil infiltration are associated with worse prognosis in cancer and may also have predictive value in patients treated with immunotherapy. Increases in IL-8 serum levels can be attributed to various sources, including the surrounding stromal tissue, immune cells in the TE and tumor cells.
A recent retrospective study in over 1300 patients showed that an elevated serum IL-8 is associated with poor outcome in patients treated with immunotherapy. Elevated serum IL-8 was also found to be negatively associated with tumor IFNy and T-cell infiltration signatures in the transcriptome.
Additionally, serum-IL8 can easily be measured in conventional blood specimens

in clinical settings, making it a potentially useful, but also broadly implementable biomarker. In colorectal cancer specifically, several studies have demonstrated that IL-8 and its receptor CXCR2 are the most significantly upregulated chemokines.
Based on these data, the combination of PD-1 blockade with IL-8 blockade could have synergistic antitumor activity, increasing the potential of response to anti-PD1 and decreasing the risk of resistance. Also, the combination of nivolumab plus anti-IL8 in 120 patients was very well-tolerated with limited toxicity and only 5% grade 3-4 treatment-related adverse events.
As soon as 30 patients have been included in the original MSS cohort (nivolumab plus ipilimumab), the next cohort will be opened. Depending on efficacy in that cohort, and the safety of the combination, expansion to triplet therapy and/or other combinations may be considered.

Rationale for nivolumab/relatlimab
Lymphocyte-activation gene 3 (LAG-3) is an inhibitory checkpoint molecule that is often expressed together with PD-1 on tumor infiltrating lymphocytes (TILs), contributing to T-cell exhaustion. Relatlimab has shown promising PFS improvement in melanoma patients, compared to nivolumab alone (Tawbi et al). Very recently the combination of nivolumab and relatlimab was approved by the FDA for the first-line treatment of patients with metastatic melanoma. In addition, the response rates to neoadjuvant nivolumab/relatlimab in melanoma patients is similar to the neoadjuvant treatment with nivolumab/ipilimumab. Based on these data, it is expected that this combination will be effective in a substantial proportion of patients with dMMR colon cancer. The favorable toxicity profile compared to nivolumab/ipilimumab makes it an attractive option, especially in the neoadjuvant setting. High response rates with a better toxicity profile compared to nivolumab/ipilimumab would be an incentive to further develop registrational studies for nivolumab/relatlimab in dMMR CC patients, in addition to organ-sparing approaches for also lower risk dMMR CC.

Study objective

This study has been transitioned to CTIS with ID 2024-513314-35-00 check the CTIS register for the current data.

Primary Objective: To determine the safety and feasibility of pre-operative immunotherapy in CRC.

Additional Primary Objective for the expanded the MSI cohort: To assess efficacy of neoadjuvant ipilimumab plus nivolumab in terms of disease-free survival.

Secondary Objectives:
• To assess the major pathological response rate (MPR, <10% viable tumor rest) and complete response rate;
• To assess post-surgical outcome and infectious complications following

neoadjuvant immunotherapy;
• To find biomarkers and evaluation strategies able to accurately assess complete and near-complete responses in order to pursue organ-sparing treatment (omission of surgery) in this patient population:
o Post-treatment CT-scans: can we use radiomics to accurately assess complete and near-complete response?
o Post-treatment MRI scans (pilot, possibly additional pilots with novel PET-tracers): is assessment of complete response rate more accurate with MRI (and/or PET) than CT-scans?
o ctDNA analysis: can we use ctDNA to assess complete response and is there a difference between complete and near-complete response in terms of minimal residual disease on ctDNA and risk of relapse?
• To expand current translational analyses, in terms of:
o RNA sequencing and inflammatory signatures to validate current findings and identify predictors of response in pMMR tumors.
o Analysis of immune cell infiltration and the difference with inflamed pMMR tumors pre- and post-treatment: why is there no pathological response in pMMR tumors showing immune activation?
o ctDNA analysis: can we predict complete and near-complete responses and if so; can we move to omitting surgery in this patient population?
• Analysis of immune cell infiltration and the difference with inflamed pMMR tumors pre- and post-treatment: why is there no pathological response in pMMR tumors showing immune activation? And the differences between complete and near-complete responders?
• To assess the immunogenic mutational load by DNA WES and correlation with putative markers of response;
• To assess relapse free survival for the MSS cohort;
• To explore the immunogenicity and in vitro T-cell sensitivity of tumor organoid cultures and explore efficacy of novel treatment combinations for a selection of patients;

Translational Objectives:
* To analyse expression and changes in expression of immune cell subsets, including but not limited to CD4+, CD8+, FOXP3+ regulatory T cells, MDSCs);
* To assess changes in immune suppressive pathway and inflammation signatures, IFNy induced gene expression and the added effects of COX2-i when combined with nivolumab and ipilimumab;
* To assess serum-IL8 and its predictive value in response to nivolumab plus ipilimumab, and to anti-IL8 + nivolumab
* To assess safety and feasibility of neoadjuvant immunotherapy and the effects hereof on post-surgical outcome and complications;
* To analyse gain/change in presence of other biomarkers and immune checkpoints, (depending on material availability for comparison); To analyse clonality and changes in the TCR repertoire pre- and post-therapy in the subset of patients showing significant changes in the TME;
* To identify subtypes of MSS CRC with signs of response and find predictive biomarkers based on IHC or gene expression analyses as mentioned above;

* To assess immunogenic mutational load by DNA WES;
* To explore the association between microbiota composition and treatment outcomes and the effect of neoadjuvant nivolumab plus ipilimumab on the gut microbiota composition;
* To identify and explore the predictive value of checkpoint expression, cytokines and chemokines, CRP/ESR/LDH/CEA;
* To evaluate and explore post-immunotherapy effects on draining lymph nodes using resection material;
* To explore the immunogenicity of autologous tumor organoids and their T cell reactivity in vitro, using normal tissue organoids as controls;
* To explore the phenomenon of exhausted T cells (Tex) by assessing IHC and gene expression signatures and combinations thereof;
* To assess ctDNA before and during therapy and after resection of the primary tumor and during follow-up;
* To explore changes in inflammation signatures, immune checkpoints, immune suppressive pathways and IFN* induced gene expression by using RNA sequencing.

Study design

DMMR cohort 3: In this multi-center, open-label phase II study, we will enroll 70 patients in the dMMR cohort after accrual of the first 30 patients in the original dMMR cohort, making a total of 100 patients with dMMR tumors to be analyzed together for disease-free survival. The study was amended to include these additional patients, including a formal sample size calculation and primary endpoint of 3-year disease-free survival (DFS) for this group.

DMMR Cohort 6: nivolumab + relatlimab: will enroll 19 patients in stage I, and with more than 14 responders accrual can continue into stage 2 for an additional 40 patients, making 59 total. Power calculation was performed using a one-sided alpha of 0.05 and power of 80%. The study will be considered a success when more than 46 pathologic responses are observed in the total cohort of 59 patients.

PMMR cohorts:
For the pMMR subgroup accrual will be continued until 30 patients have been treated with nivolumab plus ipilimumab after which additional amendments can be done to include other treatment combinations.
New cohorts (4 and 5)

For the pMMR/MSS cohort, after accrual of 30 evaluable patients has been complete:
- cohort 4: in which patients will receive nivolumab plus anti-IL8 (BMS-986253)
- cohort 5: in which patients will receive nivolumab plus relatlimab (anti-LAG3)
- additional cohorts will open depending on the possibility of new treatment combinations

Intervention

Patients will be treated with short-term immunotherapy + COX2-inhibitors. This treatment will be given during the window period until surgical resection of the tumor. The duration of treatment will be approximately 4 weeks.
After completion of accrual, analysis of the primary endpoint will be performed. Based on these findings and available compounds at that time, the study will be amended to include new drug combinations with one or more of the study drugs used in the first group of patients.

For the MSI subgroup, analysis of disease-free survival will be performed 6 months after inclusion of the last patient.
Analysis of pathological response rate may be presented or published prior to DFS data.

Patients with MSI tumors will be treated with a single dose of ipilimumab 1mg/kg on day 1 and two cycles of nivolumab 3mg/kg on day 1 and 15, respectively.
Patients with MSS intumors in group 1 will be treated with a single dose of ipilimumab 1mg/kg on day 1 and two cycles of nivolumab 3mg/kg on day 1 and 15, respectively. Additionally, patients with MSS tumors will be randomized to receive celecoxib 200mg once daily until the day before surgery (group 2), until accrual of 30 patients within the MS subgroup has been completed, after which the study may be amended to include new treatment combinations for the MSS group.The next cohort for the pMMR/MSS group of patients will consist of nivolumab 3mg/kg plus BMS-986253 (anti-IL8) 2400mg on day 1 and 15.

A minimum of 12 tumor biopsies is required at baseline, acquired through colonoscopy. Tumor and normal tissue will be collected at resection. One CT scans will be required at baseline and post-treatment, prior to surgery. Blood draws (incl. PBMC, serum and plasma collection) will be required at baseline, before every cycle of therapy, peri-operatively and.during follow-up.

Extra blood samples taken:
- all new inclusions
- 20ml per sample extra for ctDNA en PBMCs
- Time points: 3, 6, 12, 24, 36, 48, 60 months.

In cohorts 5 and 6, patients will be treated with a combination of nivolumab and relatlimab.
Cohort 5: patients with MSS tumors will be coadministered nivolumab and relatlimab at a flat dose of 240/240mg
Cohort 6: patients with MSI tumors will be coadministered nivolumab and relatlimab at a flat dose of 480/480mg

Study burden and risks

Currently, no it is not standard of care to give pre-operative treatment is given to patients with colon cancer. However, based on the FOXTROT data national guidelines for the treatment of colon cancer will advise consideration of neoadjuvant chemotherapy when atu T4 tumor is suspected. There are no specific advices with regards to MSI or MSS tumors yet, awaiting the next update of these guidelines and incorporation of the FOXTROT data for MSI tumors after publication (considering the lack of pathological response in most patients with MSI tumors). Post-operative adjuvant chemotherapy is commonly administered to patients with stage 3 tumors and in some high risk cases in stage 2 tumors (only MSS), and has been shown to marginally increase PFS and OS, the latter by approximately 5%.

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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Signed written informed consent;
• Patients at least 18 years of age;
• Non-metastatic adenocarcinoma of the colon (and rectosigmoid considered as non-rectal and not undergoing neoadjuvant treatment)
o No signs of distant metastases on CT-scan and physical examination;
o dMMR cohorts 3+6: >cT3 and/or N+
• No clinical obstruction;
• No clinical symptoms or radiological suspicion of perforation;
• Colonoscopy must be performed after informed consent to obtain study-specific biopsies. If biopsies are not possible, patients cannot be included in the study;
• WHO performance status of 0 or 1;
• Screening laboratory tests must meet the following criteria and should be obtained within 7 days prior to randomization/registration: WBC > 2.0 x 10^9/L, ANC > 1.5x10^9/L, platelets > 100 x 10^9/L, Hemoglobin > 5.0mmol/L. Transfusion is allowed to obtain an adequate hemoglobin level. Liver function tests: total bilirubin
< 1.5 upper limit of normal (ULN) (except for subjects with Gilbert syndrome, who can have total bilirubin <3.0 mg/dL); alkaline phosphatase <2.5 ULN;

transaminases (ASAT/ALAT) <3 x ULN; LDH < 2 x ULN;
• Creatinine clearance (Cockcroft-Gault) of >40 ml/min;
• Women of childbearing potential (WOCBP)* must use appropriate method(s) of contraception. WOCBP should 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;
• Women of childbearing potential 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 nivolumab;
• Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception;
• CT-scan must be performed within 28 days prior to registration;
• No previous treatment with immune checkpoint inhibitors targeting including but not limited to CTLA-4, PD-1 or PD-L1;
• No previous treatment with chemotherapy for colon cancer.
o For dMMR cohort no previous chemotherapy for any malignancies
• No radiotherapy prior to or planned post-surgery radiotherapy for disease under study;
• No active malignancies other than disease under study within 3 years prior to inclusion, except for malignancies with a negligible recurrence rate (e.g. <10% in 5 years);
• Allergies and Adverse Drug Reaction
o No history of allergy to study drug components
o No history of severe hypersensitivity reaction to any monoclonal antibody
• No intercurrent illnesses, including but not limited to infections, unstable angina pectoris;
• No underlying medical conditions that, in the Investigator*s opinion, will make the administration of the study drug hazardous or obscure the interpretation of toxicity determination of adverse events;
• No positive test for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection;
• No active autoimmune disease or a documented history of autoimmune disease, or other medical conditions requiring systemic steroid or immunosuppressive medications, except for subjects with vitiligo, diabetes mellitus type 1, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis or resolved childhood asthma/atopy not requiring systemic treatment;
• No conditions 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;
• No live vaccines in the 4 weeks prior to inclusion;

• No history of uncontrolled medical or psychiatric illness;
• No psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule;
• No current pregnancy or breastfeeding

Exclusion criteria

• (No) previous treatment with immune checkpoint inhibitors targeting CTLA-4, PD-1 or PD-L1;
• No radiotherapy prior to or planned post-surgery radiotherapy within this trial;
• Allergies and Adverse Drug Reaction
O No history of allergy to study drug components
O No history of severe hypersensitivity reaction to any monoclonal antibody
O No history of allergy or severe hypersensitivity to NSAIDs or COX2-I (MSS tumors)
• No intercurrent illnesses, including but not limited to infections, unstable angina pectoris
• No positive test for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection;
• No live vaccines in the 4 weeks prior to inclusion;
• For patients with MSS tumors: no current use of NSAIDs or COX2-inhibitors at registration and no active peptic ulcer, gastrointestinal bleeding, unstable ischemic heart disease of thrombus etiology or significant established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease;
• No underlying medical conditions that, in the Investigator*s opinion, will make the administration of the study drug hazardous or obscure the interpretation of toxicity determination of adverse events;
• No active autoimmune disease or a documented history of autoimmune disease, or other medical conditions requiring systemic steroid or immunosuppressive medications, except for subjects with vitiligo, diabetes mellitus type 1, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis or resolved childhood asthma/atopy not requiring systemic treatment;
• No conditions 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;
• No history of uncontrolled medical or psychiatric illness;
• No psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule;
No current pregnancy or breastfeeding;

• No active malignancies other than disease under study within 3 years prior to inclusion, except for malignancies with a negligible recurrence rate (e.g. <10% in 5 years).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-03-2017
Enrollment:	268
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-986016
Generic name:	Relatlimab
Product type:	Medicine
Brand name:	BMS-986253
Generic name:	HuMax-IL8
Product type:	Medicine
Brand name:	celebrex
Generic name:	celecoxib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	opdivo

Generic name:	nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-09-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-11-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2019

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-12-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2024-513314-35-00
EudraCT	EUCTR2016-002940-17-NL
CCMO	NL58483.031.16