A phase 1 study of oral Debio 0123 in combination with carboplatin in patients with advanced solid tumors.

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This study has been transitioned to CTIS with ID 2024-510984-52-00 check the CTIS register for the current data. Main Objective : - Dose escalation part: To determine the recommended phase 2 dose (RP2D) of Debio 0123 when administered in combination...

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

Summary

ID

NL-OMON56391

Source
ToetsingOnline

Brief title
Phase I dose-finding study of Debio 0123 in combination with carboplatin.

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced Malignancy / Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Debiopharm
Source(s) of monetary or material Support: Debiopharm International SA;industry

Intervention

Keyword: Advanced Solid Tumor, Debio0123

Outcome measures

Primary outcome

Dose escalation part: RP2D of Debio 0123 when administered in combination with carboplatin.

Expansion part: Safety and tolerability: Incidence of treatment-emergent SAEs, incidence and severity of TEAEs and laboratory abnormalities graded according to NCI-CTCAE version 5.0 criteria, incidence of treatment discontinuations and treatment modifications dut to AEs and laboratory abnormalities, change in vital signs, ECG, and ECOG PS. Preliminary anti-tumor activity: Tumor response according to RECIST version 1.1: ORR.

Secondary outcome

Dose escalation part:

- Occurrence of DLTs

- Incidence of treatment-emergent Serious Adverse Events (SAEs)

- Incidence and severity of treatment-emergent adverse events (TEAEs) and laboratory abnormalities, graded according to NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 5.0 criteria

- Incidence of treatment discontinuations and treatment modifications due to AEs and laboratory abnormalities

- Change in vital signs, ECG, and ECOG PS (Eastern Cooperative Oncology

Group performance status)

- For Arm A, PK parameters of Debio 0123 in monotherapy in plasma and urine after
single dose on Cycle Day -3 and following 3 days of dosing
(i.e. after the morning dose on Cycle 1 Day 3)
- For Arm A, PK parameters of Debio 0123 and carboplatin in combination after the morning dose of Debio 0123 on Cycle 2 Day 1.
- For Arm B, PK parameters of Debio 0123 and its metabolite on Cycle 1 Day 1 and Cycle 1 Day 10, i.e. after the first and last dose of the first cycle
- For Arm B, PK parameters of carboplatin (concentration of free platinum in plasma and other PK parameters as deemed appropriate) on Cycle 1 Day 1
- For Arm B, PK parameters of Debio 0123 and its metabolite on Day 10 of Cycle 2 (fed state) and Cycle 3 (high gastric pH with concomitant lansoprazole), compared to PK parameters on Day 10 of Cycle 1 (fasted state and normal gastric pH conditions)
- Relationship between plasma concentration of Debio 0123 (and its metabolite) and changes in QTcF
- Tumor response according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria: best overall response (BOR), overall response rate
(ORR), disease control rate, best change in tumor size
- Median and 1- and 2-years rates of progression-free survival (PFS) and OS

Expansion part:

- BOR, disease control rate, according to RECIST version 1.1, and best change

in tumor size

- Duration of response (DOR), time to progression (TTP)

- Median PFS

- PK parameters of Debio 0123 (and of its metabolite) (including, but not

limited to, Ctrough and AUC0-t, as applicable) over the first 2 cycles.

Study description

Background summary

Currently, limited emerging clinical data are available with Debio 0123. The study design has been based on the extensive nonclinical investigations in vitro and in vivo, summarized below. Please refer to the Debio 0123 Investigator*s Brochure for a comprehensive presentation of all available data.
1. Pharmacology
Debio 0123 is a potent and highly selective WEE1 inhibitor shown to decrease phosphorylation of WEE1 target CDK1 in cell lines and induce increased mitosis as well as unrepaired DNA damage.
In vivo, Debio 0123 has shown a dose-dependent anti-tumoral activity as single agent that was well tolerated. In a lung cancer xenograft model, treatment with 30 mg/kg Debio 0123 resulted in tumor regression. In an in vivo lung cancer model, where neither Debio 0123 nor carboplatin decreased tumor growth when administered as single agents, combination of both strongly reduced tumor growth and was well tolerated, using several schedules of treatment. These data supported the further clinical development of Debio 0123 in combination with carboplatin.
2. Nonclinical pharmacokinetics and metabolism
Debio 0123 is a high permeability drug and in vitro data suggest no significant involvement of efflux transporters such as P-gp (ABCB1), BCRP (ABCG2) or MRP2 (ABCC2) for its intestinal transport. Significant systemic exposure was observed in animals (mice, rats, monkeys) after oral administration of Debio 0123 (oral bioavailability 66-100%), and nonclinical PK properties (half-life of 4.5-7.5-hours [h] across the 3 species, resulting from a medium clearance and high volume of distribution) support to start with a once-a-day (QD) dosing regimen in this FIH study. Neither gender effect nor food effect was observed in the rat. Debio 0123 is moderately bound to plasma proteins (92% in humans).

Extensive distribution into tissues and into the tumor (tumor:plasma ratio 9.2) was confirmed in the mouse, with significant brain penetration (brain:plasma ratio 0.7-1.3).

Analyses of urine from the animal PK studies showed that renal excretion is marginal (< 1% of the dose excreted as unchanged Debio 0123 in urine), and in vitro data suggest that Debio 0123 is mainly metabolized in the liver and intestines by CYP3A4. Based the in vitro and in vivo metabolism studies, the major metabolite in animals was identified as N32-desmethyl-Debio 0123 (AUC compared to the parent compound: 7.5-23.6% in the mouse; 3.2-16.7% in the rat; 44.3-54.1% in the monkey), which retains an in vitro WEE1 inhibiting activity similar to that of the parent drug, although less cell permeable. Although the in vitro interspecies metabolite profiles have suggested that it may be formed only to a lower extent in humans, the PK of this metabolite will be investigated in the FIH study.
Based on in vitro studies evaluating the risk of drug-drug interactions, Debio 0123 has shown significant potential to inhibit CYP2C19 and CYP3A4 (and, albeit to a lesser extent, CYP2C8), as well as transporters P-gp (ABCB1), BCRP (ABCG2), OCT1, OCT2, MATE1 and MATE2-K. Signs of CYP3A4 induction were also observed. In vivo significance remains to be further evaluated and will depend on the dose administered and actual exposure achieved in humans. Nevertheless, those data have formed the basis for recommendations regarding the use of concomitant medications in the FIH study. Of note, PK interaction from Debio 0123 on carboplatin was not expected since carboplatin PK is neither dependent on hepatic metabolism nor on active renal secretion.
3. Nonclinical safety
A nonclinical safety program has been conducted consisting of 7-, 14-, and/or 28-day repeat dose toxicity in two relevant species, rats and monkeys, with a recovery phase and including exposure assessment to Debio 0123 and its major metabolite.
In the rats, repeated administration of 50 mg/kg/day was not tolerated over 14 days in the MTD (maximum tolerated dose) study and well tolerated at 30 mg/kg/day over 28 days in the GLP (Good Laboratory Practice) study. Clinical chemistry pointed towards regenerative anemia (decreased red cell production and increased reticulocytes) and liver effects (enzyme elevations). In the latter organ, histopathologic findings were limited to minimal centrilobular hypertrophy. Adrenal cortical hypertrophy alongside thymus atrophy was considered as stress reaction due to administration. In the lungs, alveolar inflammatory cell infiltration was noted in both sexes and in the prostate of males a decreased secretion, in line with a decreased organ weight. Organ weight increases in liver, spleen and adrenal glands were considered due to extramedullary hematopoiesis. In females, kidney and heart weights were also increased with no histopathological correlates. Additional histopathology of the mid- and low-dose groups and recovery animals is currently ongoing, but due to the limited effects already seen in the high-dose animals, the Severely Toxic Dose in 10% of the animals the Severely Toxic Dose in 10% (STD10) of the animals was was considered to be above the highest dose level of 30 mg/kg/day

in this 28-day GLP study in rats.
In the monkeys, 30 mg/kg/day were not tolerated during a 14-day MTD study. The animals in this group were sacrificed on Day 12 due to their body weight loss.
In the GLP study with a high-dose level of 10 mg/kg/day, treatment with Debio 0123 was well tolerated at all dose levels. The findings were limited to hematology and clinical chemistry (regenerative anemia and liver enzyme elevations), with low severity and showing recovery. No histopathological observations were made. In male monkeys only, slight increases in the QTc interval were noted from 3 mg/kg/day, but did neither increase further with 10 mg/kg/day, nor following the 2-fold increase in Cmax due to accumulation after 14 days of treatment. In addition, a minimal decrease of the respiratory rate was noted in the monkey telemetry study at 10 mg/kg/day. In conclusion, the Highest Non-Severely Toxic Dose (HNSTD) was not reached in this study.
Alongside the classical nonclinical safety assessment of Debio 0123, cardiac safety was investigated extensively based on initial results on the human Ether-a-go-go-Related gene (hERG) ion channel (IC50 9 µM) and effects on stem-cell derived human cardiomyocytes (severe electrophysiological changes from 3 µM). In addition to hERG, Debio 0123 inhibits to some extent the voltage-gated L-type Calcium channel (Cav1.2 - IC50 ~30 µM) and also the voltage-gated Sodium channel (Nav1.5 - IC50 ~30 µM). Of note, the identified metabolite N32-demethyl-Debio 0123 showed similar IC50 values for each of the 3 ion channels. Though such concentrations will likely not be reached systemically in vivo, the possible slight effects on these channels may contribute to the overall cardiac effect. A monkey telemetry study showed clear QT prolongations, but these were limited and not dose-dependent (no relevant increase in the QT duration at dose levels above 10 mg/kg/day). Experiments in tissues and cardiomyocytes obtained from human donor hearts confirmed the potential of Debio 0123 to increase the QT duration but did not show pro-arrhythmic signals. In addition, Debio 0123 showed a potential for a negative inotropic effect. Debio 0123 was not directly mutagenic but positive in the rat micronucleus assay, which is expected based on its mechanism of action of interfering with cell cycle progression control.
Debio 0123 absorbs in the ultraviolet-visible spectrum and was positive in the in vitro 3T3 Neutral Red Uptake (NRU) photosafety assay. As a consequence, Debio 0123 may induce phototoxicity in humans. Based on these results, a phototoxic effect of Debio 0123 cannot be excluded. Since no further data on the accumulation of Debio 0123 in the skin is available, as a precautionary measure, subjects must be advised to avoid excessive exposure to sunlight an

Study objective

This study has been transitioned to CTIS with ID 2024-510984-52-00 check the CTIS register for the current data.

Main Objective :
- Dose escalation part: To determine the recommended phase 2 dose (RP2D) of Debio 0123 when administered in combination with carboplatin in subjects with

solid tumors which recurred or progressed after prior cisplatin or carboplatin containing therapy.
- Expansion part:
To characterize the safety and tolerability of Debio 0123 when administered in combination with carboplatin at the RP2D determined during the dose escalation part of the study and to evaluate the preliminary antitumor activity of Debio 0123 when administered in combination with carboplatin.

Secondary objectives:
- Dose escalation part :
1.To determine the dose-limiting toxicities (DLTs) of Debio 0123 when administered in combination with carboplatin
2.To characterize the safety and tolerability of Debio 0123 when administered as monotherapy (Arm A) and in combination with carboplatin (Arm A and Arm B)
3.To determine the pharmacokinetic (PK) profile of Debio 0123 (and of its metabolite N32-desmethyl-Debio 0123) when administered alone (Arm A) and in combination with carboplatin (Arm A and Arm B)
4. For Arm B, to assess the effect of food and high gastric pH (concomitant lansoprazole) on the PK of Debio 0123
5.To evaluate the relationship between plasma concentrations of Debio 0123 (and its metabolite) and changes in QT interval corrected using Fridericia's formula (QTcF, C-QTcF relationship)
6.To make a preliminary assessment of anti-tumor activity of Debio 0123 when administered in combination with carboplatin in subjects with solid tumors progressed after prior cisplatin or carboplatin containing therapy
- Expansion part:
1. To assess additional parameters relative to the preliminary antitumor activity of Debio0123 when administered in combination with carboplatin.
2. To confirm the PK profile Debio 0123 (and its metabolite N32-desmethyl-Debio 0123) when administered at the RP2D in combination with carboplatin

Study design

Multi-center, open-label, non-randomized, uncontrolled, study with a dose escalation part of Debio 0123 as monotherapy and in combination with carboplatin, in subjects with advanced solid tumors that recurred or progressed following prior cisplatin or carboplatin-containing therapy, and for which no standard therapy of proven benefit is available. The dose escalation part will be followed by an expansion part of Debio-0123 in combination with carboplatin in subjects with platinum-resistant, recurrent epithelial ovarian cancer (EOC), primary peritoneal cancer, or fallopian tube cancer.
The dose escalation part consists of 2 arms testing each a different regiment,. Arm A includes Debio 0123 as monotherapy (first cycle only) and in combination with carboplatin (starting with Cycle 2 until end of treatment [EOT]), and Arm B Debio 0123 in combination with carboplatin (starting at cycle 1 until EOT) .
The dose escalation part will follow an adaptive dose-escalation design using a modified Continual Reassessment Method (mCRM).

The expansion part of the study will start after the recommended phase 2 dose (RP2D) has been determined in the dose escalation part. The study population will consist of subjects with platinum-resistant, recurrent, histologically or cytologically confirmed high-grade (serous, clear cell, or endometrioid) EOC, primary peritoneal cancer, or fallopian tube cancer. The subjects will receive Debio 0123 in combination with carboplatin starting at Cycle 1 and continue treatment until EOT.

Intervention

Debio 0123 is formulated for oral administration in capsules of 20 mg, 30 mg, 60 mg, 100 mg, 130 mg and 150 mg strength (10 mg mini-tablets in hard gelatin capsules)
Carboplatin: concentrate for solution for infusion.

Study burden and risks

When participating to the study, patients enrolled in arm A will have to visit the study sites during the screening period (on 2 consecutive days), cycle 1 (13 times), cycle 2 (6 times), and cycles 3 and all subsequent cycles (also 6 times per cycle), for receiving the study treatments (Debio 0123 is administered on day -3 of cycle 1, then on days 1 to 3 of each cycle. Carboplatin is infused on day 1, starting from cycle 2 onwards).

Patients enrolled in arm B will have to visit the study sites during the screening period , and all cycles (13 times, visits on site may be reduced up to 7 times), for receiving the study treatments (Debio 0123 is administered on day 1, 2, 3, 8, 9 and 10 of each cycle, Carboplatin is infused on day 1).

Patients enrolled in expansion part have to visit the study sites during the screening, then all cycles (13 times, visit on site my be reduced), for receiving the study treatments (Debio 0123 is administered from D1 to D3 (and from D8 to D10 for some patients), carboplatin is infused on D1 or each cycle)
A visit for tumor assessment to be performed at cycle 3 and 5 and then once every third cycle (from C5 anwards).
Visits of the patients at the study site will enable the monitoring of their condition by the medical staff (e.g. cardiac function monitoring, testing of laboratory parameters). In addition, during these visits, additional biological samplings will be performed for pharmacokinetics, pharmacodynamics, pharmacogenetics and biomarkers studies (samples related to pharmacokinetics taken during all cycles, only during cycle 1 for other studies).
For patients in Arm A, starting at cycle 3 and then every 2 cycles, patients will undergo CT-scans or MRIs on day 21 to evaluate tumor response to the study treatment.
For patients in Arm B, at screening and EOT visit; at Day 21 of Cycles 3 and 5 and at the end of every three cycles for up to 2 years from the first drug

intake patients will undergo CT-scans or MRIs.
For patients in expansion part, patients will undergo CT-scans or MRIs at screening, Cycle 3 D21 and Cycle 5 D21 and at D21 of every third cycle after Cycle 5 for up to 2 years after Cycle 1 D1, EoT, and efficacy FU, every 12 weeks, if applicable.

This will also be the case at the end of treatment and then during follow-up study visits (will be scheduled every 3 months if treatment is discontinued before the maximum duration of 2 years for other reasons than disease progression and until the patient is receiving another anti-cancer treatment, and this until a maximum of two years after study treatment initiation).
Female patients will be tested for pregnancy during screening, on day -4 of cycle 1 (baseline), then on day 21 of each subsequent cycles, and finally at the end of treatment and 30 days after.

Moreover, participating patients will be exposed to the following main risks:
1. associated to Debio 0123 intake: QT prolongation, reduced number of red blood cells (which can cause tiredness and shortness of breath), reduction in the number of platelets in the blood, which increases the risk of bruising and bleeding (thrombocytopenia), elevation of one type liver enzyme named alanine aminotransferase and fatigue.
2. associated to carboplatin intake: hematological toxicity (leukopenia, neutropenia, thrombocytopenia and anemia), myelosuppression, hepatic and/or renal insufficiency, allergic reactions, neurotoxicity, ototoxicity and tumor lysis syndrome.
3. associated to the combination of Debio 0123 and carboplatin, even if an increased risk of side effects when both treatments are combined is not expected. However, because it has not been proved in humans yet, this cannot not be excluded. For this reason, special precaution will be taken when Debio 0123 and carboplatin will be administered in combination, to monitor the presence of the following side effects: Cardiotoxicities, hematological and gastro-intestinal toxicities.
4. Risks associated to lansoprazole are specified in the product label
5. associated to study procedures:
a. Venipuncture may cause local swelling, pain, redness, bruising, and seldom infection.
b. Use of contrast agents for echocardiograms, CT-scans, MRIs, may cause allergic or cardiopulmonary reactions.
c. Exposure to higher levels of radiation compared to natural environment when undergoing CT-scans, however with a low risk of harmful effects.
d. Skin punch or tumor biopsies: invasive procedures may cause pain, bleeding, infection, damage to nearby tissue or nerves, reaction to local anesthetic, irritation and swelling at the site, bruising, scarring, moving cancer cells into unaffected areas (very rare).
Based on preclinical results, development of a similar compound and medical need for these patients, we evaluate the potential benefit as the following:
Debio 0123 exhibited a potent anti-tumoral activity as a single agent and

showed promising synergistic effects when combined with a DNA damaging agent like carboplatin. In addition, the mechanism of action of Debio 0123 within the cell cycle and preliminary clinical results with a similar molecule (the WEE1 inhibitor AZD1775), support the likelihood that patients may benefit from the treatment combining Debio 0123 and carboplatin, particularly in the absence of a standard therapy of proven benefit.
Because of the urgent medical need of these recurrent solid tumors, the strategy of this FIH study is to create an appropriate balance between potential risks and benefit of Debio 0123. Although there is no evidence that the experimental drug will be providing benefit to the patients, it is in the interest of these patients to provide them with a drug that might contribute to improve their life expectancy.

Contacts

Public
Debiopharm

Forum "Après-demain", Chemin Messidor 5-7
Lausanne 1006
CH
Scientific
Debiopharm

Forum "Après-demain", Chemin Messidor 5-7
Lausanne 1006
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Dose escalation part:
1.Histologically or cytologically confirmed locally advanced or metastatic solid and non-bleeding tumors that had recurred or progressed following standard therapy, has not responded to standard therapy or for which no standard therapy of proven benefit is available.
2. In addition, for Arm B of the dose escalation part only: The subject should be willing to comply with the requirements for the food effect high gastric pH (lansoprazole) investigations and have no contraindications to these requirements.

Expansion part:
1. Platinum-resistant, recurrent, histologically or cytologically confirm high grade (serious, clear cell, or endometrioid) EOC, primary peritoneal cancer, or fallopian tube cancer.
2. Measurable disease per RECIST version 1.1.
3. Documented progressive or recurrent disease according to RECIST version 1.1 since the last anti-cancer therapy and prior to study entry.
Patients with CA-125 progression in the absence of measurable disease will NOT be eligible.

Both dose escalation and Expansion:
1.Able and willing to undergo tumor biopsy unless archived tumor sample is available.
2.Previous platinum-based chemotherapy (carboplatin or cisplatin).
3.Life expectancy of at least 3 months in the best judgement of the Investigator.
4.Adequate bone marrow, liver biochemistry, renal function and adequate coagulation status
5.Female subjects of child-bearing potential must have a negative serum pregnancy test at screening and be willing to practice the following highly effective contraception methods from the time of study entry up to 6 months after the last day of treatment:
Male subjects must agree to use a condom from study entry and up to 6 months after the last day of treatment. The subject's female partner should use highly effective contraception methods, which may include oral contraceptives or any of the methods outlined above, during this period.

Exclusion criteria

1.History of other malignancies requiring active treatment in the last 6 months.
2.Brain tumors and/or brain metastases unless they are asymptomatic, stable on recent imaging (not dated more than 30 days from the inclusion date) and have

not required active treatment in the last 3 months.
3.History of myocardial infarction or stroke within 6 months, congestive heart failure greater than New York Heart Association (NYHA) class II, unstable angina pectoris, unexplained recurrent syncope, cardiac arrhythmia requiring treatment or family history of sudden death from cardiac-related causes before the age of 50, any cardiotoxicity experienced after previous chemotherapy.
4. Left ventricular ejection fraction (LVEF) below the normal range (< 55%)
5.Baseline Fridericia's corrected QT (QTcF) interval greater than 470 ms (female) or greater than 450 ms (male), history of congenital long QT syndrome, the presence in the screening ECG of a conduction abnormality that in the opinion of the Investigator would preclude safe participation in this study.
6.Concomitant use of a drug with a known risk of QTc. If such a drug has been used by the subject, a wash-out period of at least 5 half-lives of the drug must occur before the first administration of study treatment.
7. Concomitant use of a drug or herbal product that is an inhibitor or inducer of CYP3A4, orr concomitant use of any drug(s) on the prohibited medication list (provided in Section 6.5.3). If such a drug has been used by the subject, a wash-out period of at least 5 half-lives of the drug must occur before the first administration of study treatment. For irreversible CYP inhibitors and CYP inducers, a 4-week wash-out period must be applied.
8.Known infection requiring the systemic use of, for example, an antibiotic or antiviral agent.
9.Pregnant or lactating woman with positive pregnancy test result
10.Chemotherapy, monoclonal antibodies/biologics, radiotherapy with curative intent or coronavirus disease-19 (COVID-19) vaccine within 28 days prior to starting study treatment. Treatment can start earlier if toxicities from previous treatment(s) are reduced to grade 1, and the investigator judges that treatment cannot wait. Palliative radiation for pain relief is allowed up to one week prior to study treatment start.
11.Not recovered from AEs (>grade 1) or toxicities due to previous treatments
12.Hypersensitivity to carboplatin or any of the excipients
13. Subjects who are exposed to high levels of ultraviolet (UV) light, for example occupational exposure to sunlight or sun bathing
14. Immunization with live or live-attenuated vaccine within 28 days prior to study inclusion or planned injection of live or live-attenuated vaccine.
15. For dose escalation Arm B only, hypersensitivity to lansoprazole or any of the excipients

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-07-2019
Enrollment:	81
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-12-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	13-05-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	15-07-2019
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	13-05-2020
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-11-2021
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	12-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-05-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	27-09-2023
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-09-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-12-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-12-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
Other	2018-003659-39
EU-CTR	CTIS2024-510984-52-00
EudraCT	EUCTR2018-003659-39-NL
CCMO	NL68044.058.18