# A Phase 1/Randomized Phase 2 Study to Evaluate LY2603618 in Combination with Gemcitabine in Patients with Pancreatic Cancer

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The primary objective of the Phase 2 part of the study is to determine if overall survival(OS) in patients with Stage II-IV unresectable pancreatic cancer administered LY2603618 and gemcitabine combination therapy exceeds gemcitabine monotherapy OS....

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Endocrine neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON36787

**Source**
ToetsingOnline

**Brief title**
JMMC

### Condition

- Endocrine neoplasms malignant and unspecified

**Synonym**
Pancreas adenocarcinoma

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Eli Lilly

**Source(s) of monetary or material Support:** Eli Lilly

## Intervention

**Keyword:** cancer, combination, pancreas, tolerance

## Outcome measures

### Primary outcome

Overall survival (OS) is the primary outcome of interest.

Pharmacokinetic (PK) analyses will be conducted on patients who have received at least 1 dose of the study drug and have had samples collected.

All patients who receive at least 1 dose of study drug will be evaluated for safety and toxicity. The primary safety outcome will be to compare the incidence of AEs between the 2 treatment groups.

### Secondary outcome

The following secondary efficacy parameters will be summarized for each treatment group:

* Progression-free survival (PFS)

* Overall Response Rate (ORR)

* Clinical benefit rate

# Study description

### Background summary

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States (Landis et al. 1999). In 2007, it was predicted that approximately 33,370 people will die of pancreatic cancer in the United States (NCCN 2007). Despite available treatment modalities, only 1% to 4% of all patients with

pancreatic cancer will survive 5 years. Hence, incidence and mortality rates are nearly identical (Evans et al. 1997). Long-term survival is limited to those patients with resectable disease who undergo pancreaticoduodenectomy. Recently the incorporation of adjuvant treatment with gemcitabine after radical resection has proven to increase survival in this subset of patients (Oettle et al, 2007). Unfortunately, because symptoms usually develop late, more than 80% of patients present with unresectable locally advanced or metastatic disease.

Gemcitabine is currently the standard of care for locally advanced and metastaticpancreatic cancer in the United States and Europe. For the registration trial it used a doseof 1,000 mg/m2 weekly for up to 7 weeks followed by Day 1, 8 and 15 infusions every 4weeks. In the clinical practice gemcitabine is administered once weekly for 3 weeks,followed by a week of rest, at each cycle throughout the study, without the up to 7-weekinitial treatment (Tandem 2000).
Gemcitabine is now used as the reference therapy for almost all randomized clinical trialsfor the treatment of pancreas cancer, including those conducted by competitorpharmaceutical companies and cooperative groups worldwide. There are examples oflarge Phase 3 trials where gemcitabine in the control arm is administered on Days 1, 8,and 15 every 28 days as it is the proposed control arm in the Phase 2 of JMMC. Oneexample is the Eastern Cooperative Oncology Group (ECOG) randomized Phase 3 studyof gemcitabine plus 5-FU versus gemcitabine in 327 patients with advanced pancreas cancer (163 in the combination arm and 164 in the monotherapy arm) (Berlin et al. 2001).In this study, gemcitabine was also administered once weekly for 3 weeks, followed by a week of rest, at each cycle throughout the study. Median survival were 6.7 months for patients on the combination arm and 5.4 months for patients on the monotherapy arm (p=0.11, log-rank test). In another recent study patients with advanced adenocarcinoma of the pancreas were randomly assigned to receive either gemcitabine 1,000 mg/m2 and cisplatin 50 mg/m2 given on Days 1 and 15 of a 4-week cycle or gemcitabine alone at a dose of 1,000 mg/m2 on Days 1, 8, and 15 of a 4-week regimen. The efficacy and
toxicity of the control arm was similar to those reported in the pivotal trial with weekly gemcitabine for 7 weeks (Heinemann et al. 2006).

**Study objective**

The primary objective of the Phase 2 part of the study is to determine if overall survival(OS) in patients with Stage II-IV unresectable pancreatic cancer administered LY2603618 and gemcitabine combination therapy exceeds gemcitabine monotherapy OS.

The secondary objectives of the Phase 2 are:
* To characterize further the safety and toxicity profile of LY2603618 when administered after gemcitabine and to compare it to the safety profile of gemcitabine monotherapy in the advanced pancreatic cancer population.
* To estimate other time-to-event variables, such as PFS and duration of

response.To explore the percentage change in tumor size at 8 weeks and the relationship with OS.
* To document response rate per Response Evaluation Criteria in Solid Tumors (RECIST).
* To evaluate the pharmacokinetics of gemcitabine, deoxydifluorouridine
* (dFdU) and LY2603618 in combination.
* To assess biomarker responses associated with LY2603618 and gemcitabine combination:
* Incorporation of nucleoside analogs (for example, gemcitabine) into the DNA of peripheral blood cells.
* Detection of p53 in tumor tissue.
* Detection of fragmented cytokeratin 18 cleaved at Asp396 (M30 neoantigen).
* To explore the evolution of CA19.9 in patients with pancreatic cancer for each treatment group and its relation with efficacy parameters.
* To explore the pharmacogenetic of drug metabolism enzyme and transporter (DMET) polymorphisms and its relation with the PK profile, safety and efficacy.
* To perform an exploratory assessment of QTc.

**Study design**

For definitions of *enter* and *enroll,* refer to the Abbreviations and Definitions table at the beginning of this protocol. Study I2I-MC-JMMC is an open-label, multicenter, no placebo controlled Phase 1 followed by a randomized Phase 2 study of IV administration of LY2603618 in combination with gemcitabine versus gemcitabine monotherapy. The Phase 1 will include patients with solid malignancy that are unlikely to benefit from approved therapies, and are amenable to gemcitabine therapy. For Phase 2 the trial can be offered only to patients with advanced or metastatic pancreatic adenocarcinoma at first presentation or after relapse, who are considered eligible for chemotherapy with gemcitabine.

The Phase 2 part is a 2:1 randomized, open label, 2-arm study of LY2603618 in combination with gemcitabine vs. gemcitabine alone (See Figure JMMC.2). JMMC will have a total of approximately 125 patients with approximately 26 patients enrolled in Phase 1 and 99 patients enrolled in Phase 2.
All patients are intended to receive 2 cycles of therapy (8 weeks) and then be assessed for disease progression. The investigator and Lilly physician will jointly allow those patients whom have not progressed on treatment to continue on study as long as the patient is benefiting, or until one of the criteria for study discontinuation is fulfilled (see Section 4.3). Patients must be evaluated at the completion of every 2 cycles to determine whether the patient continues to benefit from treatment prior to receiving additional cycles of therapy.
All patients enrolled in the study (Phases 1 and 2) will receive gemcitabine 1000 mg/m2 as a 30-minute IV infusion, once weekly (Days 1, 8, and 15) for 3 consecutive weeks followed by 1 week of rest; repeating every 28 days (3 administrations per cycle).

Patients enrolled to the experimental arm (Arm A) in Phase 2 will receive the dose of LY2603618 as determined in the Phase 1 and in the same sequence. Patients enrolled to the control arm (Arm B) in Phase 2 will receive only gemcitabine at 1000 mg/m2 with the same weekly schedule

**Intervention**

All participating patients in this trial will receive gemcitabine intravenously over
approximately 30 minutes (maximum 60 minutes) at a dose of 1000 mg/m2 on Days 1, 8,and 15 followed by a week of rest (28 day cycle).For those patients enrolled in Phase 1 portion or randomized to Arm A in the Phase 2 portion, LY2603618 will be administered intravenously over 1 hour approximately 24 hours after the administration of gemcitabine (range 20 to 33 hours after the initiation of the gemcitabine infusion).

**Study burden and risks**

Risk Profile for LY2603618
Approval Date 2009 December 16

As of 17 November 2009, LY2603618 has been administered to 50 patients with cancer with adverse event data available from 44 patients through 02 October 2009; therefore, there is very limited safety information available for LY2603618 in humans, and the majority of the risks are based on studies in animals.
Risks and Discomforts Associated with LY2603618
LY2603618 is a drug designed to work with other chemotherapeutic (anti-cancer) agents that damage DNA (part of the cell that has all of the genetic information. LY2603618 interrupts the tumor cell*s ability to repair the damage of DNA or altered cell growth after being treated with another anti-cancer drug. When LY2603618 is administered with other anti-cancer drugs, the effect of the anti-cancer drug is expected to be enhanced. It is also possible that the toxicity of the other anti-cancer drug will be increased when LY2603618 is administered with it.
Of the 50 patients who were given LY2603618, thirty-one patients have received LY2603618 in combination with pemetrexed. Nineteen patients received LY2603618 in combination with gemcitabine.
Through 17 November 2009, twenty-one patients had events that met serious criteria (hospitalization, life-threatening, or other serious reason). Of the 21 patients, 17 patients were treated with LY2603618 in combination with pemetrexed. In 6 of the 17 patients treated with the combination of LY2603618 and pemetrexed, the events were considered possibly related to LY2603618 and pemetrexed by their study doctor. In the combination of LY2603618 with pemetrexed,1patient experienced a lung infection (pneumonia). A second patient experienced a decrease in white and red blood cells and feeling tired. The

third patient experienced an allergic-type reaction while receiving LY2603618, which produced a feeling of not being able to get air into the lungs and a rise in the blood pressure and the heart rate. A fourth patient experienced diarrhea which lasted 2 weeks. The fifth patient experienced fever and a decrease in red cells and platelets. The sixth patient was hospitalized with bleeding from the lower intestine. This patient also presented a decrease in white and red blood cells and platelets.As of 02 October 2009, all 31 patients experienced 1 or more discomforts while receiving LY2603618 and pemetrexed. The discomforts reported in more than 10% of the patients who have received at least one dose of LY2603618 are below. These adverse events might be related to LY2603618 and/or pemetrexed, the disease, other medications taken by the patient, or a combination of some or all these factors.
12 to 17 patients reported:
* Low white blood cell counts that could increase the probability of infections
* Nausea
* Feeling tired.
8 to 11 patients reported:
* Low red blood cell counts that could make you feel tired
* Constipation
* Diarrhea or loose stools
* Vomiting
* Low potassium level in blood that could cause cramps or problems with the heart
* Fever
4 to 7 patients reported:
* Low platelet count that could cause bleeding and/or bruising
* Feeling sick or discomfort in your stomach
* Swelling or water retention in the arms or legs
* Chills or feeling cold
* Fungal infection in the mouth that may cause a burning feeling or irritation in the mouth or throat
* Increased in a blood test called alkaline phosphatase which may indicate damage to your liver by treatment
* Dehydration or excessive water loss in the body
* Increased sugar in your blood
* Low magnesium in your blood which may produce weakness in your muscles
* Musculoskeletal chest pain that is not associated with cardiac pain or disorder
* Back pain
* Bad taste in mouth that may alter the taste of food or drinks
* Tremor
* Feeling short of breath
* An accumulation of fluid in the lungs
* Rash
Rare, but serious events reported in at least 1 patient; not previously listed (<10%):
* Infusion reaction that may cause shortness of breath, an increase heart rate,

and/or an increase in blood pressure
* Bleeding in the intestines
Four patients treated with LY2603618 in combination with gemcitabine experienced serious adverse events; all were considered possibly related to study treatment (LY2603618 and/or gemcitabine) by the study doctor. One of the 3 patients treated with LY2603618 and gemcitabine experienced an infusion-related reaction while receiving LY2603618 with cold sweats and low blood pressure. The second patient experienced worsening in her kidney function after several infusions of LY2603618 and gemcitabine. The third patient experienced a decrease in white blood cells which did not require any therapy. A fourth patient experienced discomfort, inflammation and clots in the vein at the infusion site after receiving LY2603618.
As of 17 November 2009, nineteen patients have been treated with LY2603618 and gemcitabine with data available from 13 patients through 02 October 2009. These patients experienced 1 or more discomforts. The discomforts reported in >10% of the patients who have received at least 1 dose of LY2603618 are below. These adverse events might be related to LY2603618, gemcitabine, the disease, other medications taken by the patient, or a combination of some or all these factors.
4 to 8 patients reported:
* Low red blood cell counts that could make you feel tired
* Nausea
* Feeling tired
* Vomiting
2 to 3 patients reported:
* Low white blood cell counts that could increase the probability of infections
* Low neutrophil cell counts that could increase the probability of infection
* Low platelet count that could cause bleeding and/or bruising
* Changes in heart rhythm that may make you feel palpitations or feelings of fainting.
* Diarrhea or loose stools
* Constipation
* Uncomfortable feeling in the stomach such as abdominal pain, upset stomach, bloating, or indigestion
* Swelling or water retention in the arms or legs
* Chills or feeling cold
* Infusion site pain
* Musculoskeletal chest pain that is not associated with cardiac pain or disorder
* Fever
* Changes in some blood tests that may reflect the drug damaging your liver.
* Increased creatinine in blood
* Lack or decrease in your appetite
* Back pain
* Headache
* Worsening of kidney function
* Cough

* Feeling short of breath
* Flushing
Rare, but serious events reported in at least 1 patient; not previously listed (<10%):
* Infusion reaction that may cause low blood pressure, and or cold sweating, and/or feeling dizzy
* Inflammation, irritation, and/or clotting of a vein just under the skin near the infusion site
Information on adverse events in animals can indicate a possible risk to people. It may be useful in your decision as to whether to participate in this study.
Animals that received LY2603618 showed harmful effects in the following parts of the body:
* Stomach and intestines, where microscopic tissue damage was seen
* Damage to the cells in the testes that form sperm
* Bone marrow (which makes red and white blood cells), where there were fewer cells present that form blood cells.
* Reversible increases in heart rate
The harmful effects seen in animals occurred with higher doses of LY2603618 than will be given to humans.
In addition, LY2603618 caused infusion or injection site injuries, where injury was noted to the blood vessel and surrounding tissues in animal studies. This infusion site injury or lesion appeared in large veins where the catheter was placed. The lesion occurred also when the compound was injected using small veins in the animal legs. In another experiment, LY2603618 also caused irritation at the skin and the tissue under the skin when LY2603618 was purposely injected under the skin outside the vein.
In humans, LY2603618 could be administered using a vein in your arm or a central catheter that may already be surgically placed in a large vein in your body. When LY2603618 is administered to humans, the infusion will be followed by a flush of fluid that does not have any drug. This will reduce the possibility of LY2603618 irritation and avoid accidental skin contact with LY2603618 that could spill while removing the needle from your arm. It is possible that you may experience discomfort, blood clot formation, bleeding, skin irritation, or other side effects related to the infusion. You should tell immediately your doctor or the nurse taking care of the infusion if you notice any discomfort around the site of the injection.
Risks in Men
While you take LY2603618:
* Do not father a child (if you are a male). If you do father a child during the study, you should immediately call the study doctor.
Risks in Women
While you take LY2603618:
* For women who could become pregnant, methods to avoid pregnancy should be taken. Tests in the lab show that LY2603618 can change DNA, and therefore LY2603618 could harm an unborn baby. You will be asked to have a pregnancy test before you are given the study drugs. You must use an effective avoidance

of pregnancy method during the study. If you become pregnant, you will no longer be allowed to take part in the study.
* Stop breastfeeding (if you are nursing a baby). It is not known if LY2603618 passes to a baby through breast milk.

Risk Profile for Gemcitabine (LY188011)
Approval Date 2007 October 24

As of 31 August 2007, 2,159,090 patients are estimated to have been treated with gemcitabine worldwide based on sales data. Over 7000 patients were treated in Lilly-sponsored clinical trials for which data are stored in the corporate database.
Risks and Discomforts Associated with Gemcitabine
Very common side effects reported by more than 10% of patients receiving gemcitabine include:
* Nausea and vomiting (feeling or being sick). These effects rarely prevent further treatment with gemcitabine and can be managed using medication.
* Decrease in white blood cells, red blood cells, and platelets. A decrease in white blood cells increases the chance of developing an infection. A decrease in red blood cells (anemia) may cause feelings of being tired. A decreased platelet count may increase the chance of bruising and bleeding after injury.
* Changes in liver function tests (tests that show how your liver is working). These changes are usually mild and non-progressive and rarely require stopping treatment with gemcitabine.
* Flu-like symptoms, including fever, headaches, chills, muscle soreness, fatigue, weakness, lethargy, loss of appetite, cough, runny nose, and sweating.
* Mild effects on the kidneys (blood or protein in the urine); diarrhoea; allergic skin rash frequently associated with itching; mild hair loss; shortness of breath; and fluid retention (usually seen as swelling of the hands, feet, or face).
Common side effects reported by between 1% and 10% of patients receiving gemcitabine include inflammation of the mucous membranes of the mouth and throat, and decreased white blood cells with fever.
Uncommon side effects reported by between 0.1% and 1% of patients receiving gemcitabine (that is, between 1 in 1000 and 1 in 100 patients) include wheezing.
Rare side effects reported by between 0.01% and 0.1% of patients receiving gemcitabine (that is, between 1 in 10,000 and 1 in 1000 patients) include a fast or irregular heart beat, decreased blood pressure, severe changes in liver function tests (including changes that may cause jaundice), severe effects on the lungs including respiratory distress (severe difficulty breathing), and severe effects on the kidneys, sometimes leading to kidney failure.
Very rare side effects reported by less than 0.01% of patients (that is, less than 1 in 10,000 patients) receiving gemcitabine include:
* Heart failure.
* Severe allergic reactions. The symptoms may include rash, changes in blood pressure, swelling and increased fluid in the tissues, increased heart rate,

difficultly in breathing, and collapse.
* Blood vessel inflammation and gangrene (death of soft tissue due to lack of blood supply).
* Severe skin reactions, including peeling of the skin.
Patients who have received radiotherapy before, during, or after receiving gemcitabine may sometimes experience side effects at the site of the radiotherapy.
Many of the side effects described above may be experienced by patients receiving other chemotherapy drugs. As with most other cancer therapies, there have been infrequent instances of death due to chemotherapy-related complications in patients who received gemcitabine.
Studies in experimental animals have shown that gemcitabine can harm the development of the embryo or fetus. This means that the use of gemcitabine should be avoided in pregnant and nursing women because of the potential of harm to the fetus.

# 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

-Histological or cytological diagnosis of adenocarcinoma of the pancreas that is locally advanced (Stage II, III) or metastatic (Stage IV) and not amenable to resection with curative intent. Patients with previous radical surgery for pancreas cancer are eligible after progression is documented. If they received adjuvant chemotherapy or chemoradiotherapy with gemcitabine, they can be enrolled if the treatment was completed 6 months before or longer.;[3] Have measurable disease or non-measurable disease, defined according to RECIST (Protocol Attachment JMMC.5).;[4] Males or females at least 18 years of age.;[5] Have given written informed consent prior to any study-specific procedures.;[6] Have adequate organ function including:
* Hematologic: Absolute neutrophil count (ANC) *1.5 x 109/L platelets *100 x 109/L, and hemoglobin *9 g/dL.
* Hepatic: Bilirubin *1.5 times upper limits of normal (ULN), aspartate transaminase (AST) <2.5 times ULN, alanine transaminase (ALT) *2.5 times ULN. If the liver has tumor involvement, aspartate transaminase (AST) <5 times ULN and ALT equaling *5 times ULN are acceptable. Patients may have endoscopic or radiologic stenting to treat biliary obstructions. If so, then bilirubin must return to <1.5 x ULN and alkaline phosphatase (AP), aspartate transaminase (AST) <5 times ULN, ALT to *5 x ULN prior to enrollment.
* Renal: Serum creatinine within normal limits, *1.5 times ULN. If the patient is enrolled using the local lab, the same local lab must be used throughout the study for dosing decisions.;[7] Have a performance status of *2 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Protocol Attachment JMMC.6).;[8] Patients may have received previous adjuvant treatment with gemcitabine with or without radiotherapy for pancreas cancer. Adjuvant treatment must have finished at least 6 months before enrolling.;[9] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.;[10] Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the trial until the patient*s physicians deems it safe to become pregnant or father a child.;[11] Females with child bearing potential must have had a negative urine pregnancy test *7 days prior to the first dose of study drug.;[13] Prior radiation therapy for treatment of cancer other than pancreatic is allowed to <25% of the bone marrow (Cristy and Eckerman 1987), and patients must have recovered from the acute toxic effects of their treatment prior to study enrollment. Prior radiation to the whole pelvis is not allowed. Prior radiotherapy must be completed at least 4 weeks before study entry.;[14] Baseline ECG QTc interval corrected by Bazett*s method (i.e., the QTc or sometimes referred to as QTcB) should be <450 msec for males and <470 msec for females.

## Exclusion criteria

-Are currently enrolled in, or discontinued within the last 28 days from, a clinical trial involving an off-label use of an investigational drug or device (other than the study drug used in this study), or concurrently enrolled in any other type of medical research judged not to be

scientifically or medically compatible with this study.
-Have serious preexisting medical conditions or serious concomitant systemic disorders that would compromise the safety of the patient or his/her ability to complete the study, at the discretion of the investigator (for example, unstable angina pectoris or uncontrolled diabetes mellitus).
-Have symptomatic central nervous system malignancy or metastasis (screening not required).
-Have current active infection that would, in the opinion of the investigator, compromise the patient*s ability to tolerate therapy.
-Females who are pregnant or lactating.
-Have known positive test results in human immunodeficiency virus (HIV), hepatitis B surface antigen (HBSAg), or hepatitis C antibodies (HCAb). Testing is not required unless circumstances warrant confirmation.
-Endocrine pancreatic tumors or ampullary cancer.
-Have previously completed or withdrawn from this study or any other study investigating LY2603618 or any other Chk1 inhibitor.
-Have known allergy to gemcitabine or LY2603618 or any ingredient of gemcitabine or LY2603618.
-Has an abnormal ECG result that would put the patient at unnecessary risk in the opinion of the investigator.
-Have conduction abnormalities, ischemic changes such as prior Qwave myocardial infarction and/or marked ischemic ST and T wave, and arrhythmias such as persistent or paroxysmal ventricular or supraventricular arrhythmias, including atrial fibrillation.

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 11-10-2011 |

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| Enrollment: | 15 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Gemzar |
| Generic name: | Gemcitabine |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | niet bekend |
| Generic name: | Chk1 Inhibitor 1 |

## Ethics review

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|---|---|
| Approved WMO Date: | 10-05-2011 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 18-05-2011 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 12-09-2011 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 04-05-2012 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 11-05-2012 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO | |

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|---|---|
| Date: | 14-02-2013 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 12-06-2013 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# 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 | EUCTR2008-006209-17-NL |
| CCMO | NL32142.018.11 |