A double-blind, randomized-withdrawal, placebo-controlled study to evaluate the efficacy and safety of human plasma-derived C1-esterase inhibitor as add-on to standard of care for the treatment of refractory antibody mediated rejection in adult renal transplant recipients

Published: 09-08-2017
Last updated: 15-04-2024

The primary objective of the study is to evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.The secondary objectives of the study are:1. To further evaluate the efficacy of C1-INH in the treatment of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50633

Source
ToetsingOnline

Brief title
N/A

Condition

- Other condition
- Immune disorders NEC

Synonym

'kidney graft rejection after renal transplant' and 'kidney not working properly after kidney transplant and not responsive to standard therapy'

Health condition

antibody-mediated kidney transplant rejection

Research involving
Human

Sponsors and support

Primary sponsor: CSL Behring LLC
Source(s) of monetary or material Support: Sponsor CSL Behring

Intervention

Keyword: Human C1-esterase inhibitor, refractory antibody mediated rejection, Renal transplant

Outcome measures

Primary outcome

Proportion of subjects with loss-of-response at the End-of-

TP2.

Loss-of-response at the End-of-TP2 is defined as any 1 of the

following 3 conditions:

* End-of-TP2 eGFR (mean of Week 36 and Week 38 eGFR)

that is not stable, defined as:

o End-of-TP2 eGFR that is < 90% of the End-of-TP1

eGFR for subjects whose End-of-TP1 eGFR (mean of

Week 11 and Week 12 eGFR) is * 100% of baseline;

o End-of-TP2 eGFR that is < 90% of baseline for

subjects whose end-of- TP1 eGFR is * 90% of baseline

and < 100% of baseline

* Allograft failure (defined by allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first)
* Subject death by any cause

Secondary outcome

Proportion of subjects with all-cause allograft failure through the Responder Follow-up Period (ie, within 48 months after enrollment). Allograft failure is defined as 1 of the following (see also Section 8.1.3.7):
* Allograft nephrectomy, institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first, OR
* Subject death by any cause.

The difference between the End-of-TP1 eGFR and baseline eGFR.

The difference between the End-of-TP2 eGFR and the End-of-TP1 eGFR.

The rate of change of eGFR during TP2 as defined by the slope of the mean regression of eGFR over time in TP2.

Time (weeks) to all-cause allograft failure through the Responder Follow-up Period (ie, within 48 months after enrollment).

Time (weeks) to all-cause allograft failure through the Responder Follow-up Period (ie, within 48 months after enrollment).

Proportion of subjects surviving through the Responder Follow-up Period.

Study description

Background summary

See protocol P26-29:

1.1 Background
Antibody-mediated rejection (AMR) is associated with poor long-term allograft and patient survival [Takemoto et al, 2004; Dalla Vecchia et al, 1997; Emonds et al, 2000; Fine et al, 1979; Stegall et al, 2011; Montgomery et al, 2011b]. Antibody-mediated rejection is mediated primarily by donor-specific antibody (DSA) directed against the human leukocyte antigen (HLA) class I and/or class II molecules present on the vascular endothelium and tubules of the transplanted kidney [Miller et al, 2004; Montgomery et al, 2011a; Pascual et al, 2008; Stegall et al, 2012; Gulleroglu et al, 2013]. This antibody-antigen interaction activates the classical complement pathway, resulting in direct cellular damage and initiation of an inflammatory response which results in further damage to the allograft [Burns et al, 2008; Grafals and Akalin, 2009; Stegall et al, 2011; Stegall et al, 2012]. Left unchecked, the endothelial damage caused by complement activation can result in allograft thrombosis, tissue necrosis, and endothelial cell detachment from the basement membrane, which are all characteristic histological features of AMR [Nguyen and Butani, 2013]. This early injury is later complicated by the proliferation of myofibroblasts leading to progressive scarring of the kidney graft [Gulleroglu

et al, 2013]. This process eventually leads to transplant glomerulopathy, as evidenced by double contouring of the glomerular basement membrane. These irreversible anatomical lesions, including intimal thickening of the peritubular capillaries (PTCs), permanently compromise allograft function [Colvin, 2007; Cornell et al, 2008; Kittleson and Kobashigawa, 2012; Nankivell and Alexander, 2010; Crespo et al, 2001; Loupy et al, 2017; Stites et al, 2015].

Clinically, patients with AMR may have fever, fatigue, irritability, pain over the allograft site, and rapid onset of renal dysfunction (decrease in urine output and estimated glomerular filtration rate [eGFR]). Several risk factors have been associated with the occurrence of acute AMR; the patients at greatest risk are sensitized (DSA+) to their donors after exposure to human HLA proteins through a prior transplant, blood transfusion, and/or pregnancy [Stegall et al, 2011; Lefaucheur et al, 2010; Eurotransplant, 2013]. Patients may also develop AMR post-transplant via (de novo) production of DSA in response to the allograft HLA proteins. Renal failure patients with DSA are generally excluded from receiving a transplant; therefore, AMR is a rare (5 to 7%), but serious and morbid complication of kidney transplantation.

There are no approved therapies for AMR; however, intravenous immunoglobulin (IVIg) therapy with plasmapheresis can successfully treat 50 to 75% of cases on the short term [Montgomery et al, 2016]. If ongoing AMR is inadequately treated, or is refractory to treatment, transplant glomerulopathy occurs. Concurrently, there is a progressive decline in renal function [Djamali et al, 2014] manifested by decline in glomerular filtration rate (GFR) until the allograft is lost and dialysis and/or re-transplantation is necessary.

Since DSA activates the classical complement pathway which results in inflammation and eventual TG, complement inhibition should prevent the damage which is associated with early graft loss. A recently completed pilot study of a human plasma derived C1-esterase inhibitor product for the treatment of AMR suggests that C1-esterase inhibitor, as an adjunct to IVIg and plasmapheresis, may protect the allograft [Montgomery et al, 2016]. Another study of complement inhibition showed that long-term suppressive therapy with a C1 esterase inhibitor product could be used to rescue patients with AMR refractory to IVIg and plasmapheresis [Viglietti et al, 2016a]. This protocol seeks to study complement inhibition by C1-esterase inhibitor in a placebo-controlled manner as a treatment for refractory AMR in renal transplant recipients.

1.2 Background Information on C1-esterase inhibitor

1.2.1 Overview

C1-esterase inhibitor belongs to the family of serine protease inhibitors. It has important inhibiting potential on several of the major cascade systems of the human body, including the coagulation, complement, and contact cascades, as well as the fibrinolytic system. In the complement cascade system C1-esterase

inhibitor inactivates its substrates by covalently binding to the active sites preventing the actions of C1r (subcomponent of complement component C1), C1s (activated form of complement component C1), and manose-associated serine proteases.
C1-esterase inhibitor is a soluble, single chain glycoprotein containing 478 amino acid residues organized into three beta sheets and eight or nine alpha helices. The heavily glycosylated molecule has an apparent molecular weight of 105 kD, of which the carbohydrate chains comprise 26% to 35%.

CSL Behring*s C1-esterase inhibitor product (*C1-esterase Inhibitor, Human [500 IU/mL]*, abbreviated as *C1-INH*) is human plasma-derived, and available at a concentration of 500 IU/mL after reconstitution. A detailed description of the chemistry, pharmacology, efficacy, and safety of C1-INH is provided in the Investigator*s Brochure [C1-INH (500 IU/mL) Investigator*s Brochure, 2017].

1.2.2 Nonclinical Evaluation
Nonclinical studies of C1-esterase inhibitor products have demonstrated an acceptable safety profile and pharmacokinetic (PK) properties.
In nonclinical studies with the currently marketed C1-esterase inhibitor product Berinert (CSL Behring), C1-esterase inhibitor was well tolerated and no toxicity was observed in single-dose intravenous (IV) toxicity studies in rats and mice at doses up to 6000 IU/kg, and in a repeated-dose IV toxicity study in rats at a dose of 200 IU/kg for 14 days [C1-INH (500 IU/mL) Investigator*s Brochure, 2017].
Local tolerance studies in rabbits were conducted with Berinert, investigating IV and subcutaneous (SC) routes of administration [C1-INH (500 IU/mL) Investigator*s Brochure, 2017]. No treatment-related local reactions were observed at IV Berinert injection sites; erythema and edema were observed at SC Berinert injection sites with a slightly higher incidence and/or intensity when compared to control sites. Overall, a single IV, intra-arterial, SC, or intramuscular injection of Berinert was locally well-tolerated in rabbits.
To investigate the thrombogenic potential of C1-esterase inhibitor products (Berinert and C1-INH), thrombogenicity studies based on the established Wessler rabbit model of venous stasis-induced thrombosis were conducted [C1-INH (500 IU/mL) Investigator*s Brochure, 2017]. Potential pro-thrombotic effects of C1-esterase inhibitor were studied following IV administration, as this route of administration leads to higher peak plasma levels, which are considered most relevant for potential pro-thrombotic effects. Following single IV administration of doses up to 800 IU/kg to rabbits, no thrombus formation could be observed.

1.2.3 Clinical Experience with C1-INH in Transplant
C1-esterase inhibitor products have been studied in kidney transplant patients for the treatment of acute AMR, prevention of AMR, and for the treatment of refractory AMR. Case reports and small clinical trials have been conducted, which suggest efficacy of C1-esterase inhibitor for the treatment of AMR in kidney transplant patients.

C1-esterase inhibitor has been evaluated for the prevention of AMR in HLA-sensitized kidney transplant recipients. A phase 1/2, exploratory, randomized, placebo-controlled, single center trial using Berinert was conducted in 20 desensitized (prior to transplant) subjects for the prevention of AMR following renal allograft transplantation [Vo et al, 2015]. Subjects received either 20 IU/kg Berinert or placebo intra-operatively (intravenously), then twice weekly for 7 doses. No subjects developed AMR in the Berinert group; 1 (10%) developed AMR in the placebo group at 1 month following treatment. At 6 months, 2 (20%) subjects developed AMR in the Berinert group; 3 (30%) developed AMR in the placebo group. Berinert was generally well tolerated in this population, with no study drug related serious adverse events (SAEs).

Another C1-INH product (Cinryze; Shire Viropharma Incorporated) was evaluated as treatment in subjects with AMR. A phase 2b, multicenter, double-blind, randomized, placebo-controlled pilot study was conducted to evaluate the use of Cinryze as add-on therapy to standard of care (ie, IVIg/plasmapheresis) in 18 subjects with acute AMR [Montgomery et al, 2016]. Subjects received IV Cinryze (n = 9) or placebo (n = 9); treatment was 5000 U (approximately 60 U/kg) IV on Day 1 then 2500 U (approximately 30 U/kg) IV every other day (6 doses) for 2 weeks for a total of 20,000 units. Both groups showed similar improvements in histopathology parameters on biopsies (Banff Classification) obtained one week after cessation of study drug (Day 20). Seven of 9 (78%) subjects receiving Cinryze and 6 of 9 (67%) receiving placebo had resolution of their AMR; the most prominent feature of the improvement on biopsy was seen as a decrease in C4d staining. Cinryze-treated subjects achieved supra-physiologic C1-esterase inhibitor levels of a median 1.73-fold above normal, and Cinryze was considered to be generally well tolerated without any serious safety concerns.

A prospective, historically matched controlled single-arm pilot study was conducted to evaluate the efficacy and safety of Berinert added to high-dose IVIg for the treatment of refractory AMR (nonresponsive to standard of care) in 6 subjects [Viglietti et al, 2016a]. Subjects received 20 IU/kg Berinert intravenously on Days 1, 2, and 3 and then twice weekly and 2 grams/kg IVIg (Privigen; CSL Behring) every month for 6 months. All Berinert-treated subjects showed an improvement in eGFR after 6 months of treatment. At Month 6, study subjects with positive C4d staining in peritubular capillaries decreased from 83% (5/6) at baseline to 17% (1/6) with treatment, and anti-HLA DSA C1q binding decreased from 100% (6/6) to 17% (1/6). No death or allograft loss was observed in patients treated with Berinert. One SAE (gastrointestinal bleeding) occurred in 1 subject, which was considered not related to the study drug. One subject experienced an adverse event (AE) of an episode of deep vein thrombosis of a lower limb 5 months after inclusion in the study, which led to discontinuation of Berinert. The episode was subsequently determined to be caused by local venous compression due to a popliteal cyst, and was considered not related to study drug.

Study objective

The primary objective of the study is to evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.

The secondary objectives of the study are:

1. To further evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.
2. To evaluate the safety of C1-INH in the treatment of refractory AMR in renal allograft recipients.
3. To evaluate the pharmacokinetics of C1-INH during the treatment of refractory AMR in renal allograft recipients.

Study design

This is a double-blind, randomized-withdrawal, placebo-controlled study consisting of 2 treatment periods, a post-treatment Follow-up Period, and Retreatment Period(s) (if needed).

Intervention

Eligible subjects will enter into the 13-week, open-label Treatment Period 1, during which all subjects will receive C1-INH. Subjects who respond to treatment with C1 INH by Week 12 as assessed by pre-defined responder criteria will be randomized into Treatment Period 2 of the study; those subjects who do not respond to treatment will enter a 45-month Non-responder Follow-up Period. Subjects who are responders will be randomized to receive either C1-INH or placebo during Treatment Period 2.

Study burden and risks

See protocol P31-32:

1.4 Potential Risks and Benefits
Consistent safety of Berinert administered intravenously for the on-demand, acute treatment of HAE attacks has been observed in over 30 years of use, with 949,282,930 IU sold worldwide for the period from 1985 and 04 August 2016. Post-marketing surveillance has shown that Berinert is safe and well tolerated when used at the recommended dosage for the treatment of acute HAE attacks. No case reports concerning proven Hepatitis A Virus, Hepatitis B Virus, Hepatitis C Virus (HCV), or Human Immunodeficiency Virus 1 or 2 infections resulting from the use of Berinert have been received.

In addition, routine use of C1-INH (500 IU/mL) for prophylaxis against HAE attacks has been studied in 2 phase 3 clinical trials in subjects with HAE. As

of 17 May 2016, 91 subjects were treated with 40 IU/kg C1-INH, 98 subjects were treated with 60 IU/kg C1-INH, and 1 subject was treated with 80 IU/kg. In total, 148 subjects received at least 1 dose of * 40 IU/kg C1-INH (combined treatments), with 85 of these subjects having a cumulative duration of exposure to C1-INH of * 1 year. The mean cumulative exposure to C1-INH over the course of both phase 3 studies combined was similar for both the 40 IU/kg and 60 IU/kg doses (39.3 weeks for 40 IU/kg; 40.3 weeks for 60 IU/kg); the single subject who was treated with 80 IU/kg received that dose for 7.1 weeks. For all subjects who received treatment with SC C1-INH twice weekly, there was no dose-dependent safety concern.

Risks associated with C1-esterase inhibitor products include hypersensitivity/anaphylactic-type reactions, thromboembolic events (TEEs), and potential virus transmission:
* Hypersensitivity/Anaphylactic-type Reactions: Hypersensitivity and anaphylactic-type reactions have been reported rarely with the use of C1-esterase inhibitor products in patients with HAE. Hypersensitivity or anaphylactic reactions in this study population are expected to be rare because the subjects have normal, physiologic C1-esterase inhibitor, as opposed to in the HAE population. Nonetheless, anaphylaxis will be specifically monitored during this study.
* Thromboembolic Events: Thromboembolic events have been occasionally reported following the use of C1-esterase inhibitor products, in particular in patients receiving off-label high doses of up to 500 IU/kg IV in the context of cardiac surgery and extracorporeal circulation. At the doses to be used in this clinical study (60 IU/kg IV; 60 IU/kg SC), a causal relationship between TEEs and the use of C1-esterase inhibitor has not been established. Nonetheless, TEEs will be specifically monitored during this study.
* Potential Virus Transmission: C1-INH contains human plasma-derived C1 esterase inhibitor and, therefore, has the potential for virus transmission to recipients. However, Berinert and C1-INH has a high margin of virus safety with the risk of virus transmission minimized by donor selection and screening criteria, and by reducing enveloped and non-enveloped viruses using pasteurization, nanofiltration methods, and chromatography [De Serres et al, 2003]. Each subject will provide a retention sample before and after treatment with the investigational product for potential future serology assessments.

Additional information on C1-INH can be found in the C1-INH investigator*s brochure [C1-INH (500 IU/mL) Investigator*s Brochure, 2017].

Without treatment, up to 90% of study subjects with refractory AMR would otherwise go on to lose their kidney graft and have associated mortality risk [Viglietti et al, 2016b]. Given the low probability of potential risks and the implementation of study procedures that will closely monitor the safety of study subjects, the associated benefit/risk assessment is acceptable for subjects who participate in the study.

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

1. Provide written informed consent and willing and able to adhere to all protocol requirements.
2. At least 18 years of age at the time of providing written informed consent.
3. Evidence of at least one DSA (to HLA class I and/or class II)
4. Recipient of a kidney transplant from an ABO compatible or ABO incompatible donor, living or deceased.
5. At least one of the following if clinical data are available:
a. Achieved a steady-state, post-transplant eGFR * 40 mL/min/1.73 m2 (as determined by local practice) within 60 days post-transplant, , OR
b. A 50% increase in urine output with a 50% decrease in serum creatinine over the first 7 days post-transplant in subjects with slow or delayed graft function.

6. Acute AMR defined per Banff 2015 criteria [Loupy et al, 2017] on pre enrollment kidney biopsy (performed within 90 days of enrollment, as the following:
a. Histologic evidence of acute tissue inflammation with presence of neutrophils and/or monocytes (g > 0, v > 0, and/or ptc > 0), AND
b. C4d positive or, if C4d negative, then g + ptc * 2.
NOTE: Subjects who have mixed cellular rejection with AMR are eligible for participation.
7. Acute AMR that is unresponsive (ie, no improvement in renal function as determined by the treating physician) after standard of care treatment:
a. If standard of care treatment is * 100 mg/kg IVIg and plasmapheresis - with or without rituximab -: * 7 days since the current AMR diagnosisat the Day 1 Visit, OR
b. If standard of care treatment is * 1 gram/kg IVIg without plasmapheresis - with or without rituximab: * 45 days since the current AMR diagnosis.
8. Subject must be willing and able to comply with the requirements of the study protocol.
9. Investigator believes that the subject understands the nature, scope and possible consequences of the study.

Exclusion criteria

1. Recipient of an en bloc kidney transplant
2. Ongoing dialysis > 2 weeks at Screening.
3. Hepatobiliary disease as indicated by 1 of the following:
a. Viral hepatitis ie, positive for HCV or HBV confirmed by nucleic acid testing (if positive, subjects
must be receiving or have received antiviral therapy and have no history of cirrhosis), OR
b. Alanine aminotransferase > 3 times upper limit of normal, OR
c. Total bilirubin > 1.5 times upper limit of normal.
4. History of human immunodeficiency virus with acquired immunodeficiency syndrome
at Screening.
5. Active bacterial or fungal infection that is clinically significant in the opinion of the investigator.
6. Not otherwise explained thrombotic microangiopathy on pre-enrollment kidney biopsy.
7. Known congenital bleeding or coagulopathy disorder.
8. Evidence of non-catheter or non dialysis access-related deep vein thrombosis, stroke, myocardial infarction, or arterial embolus within the 3 months before the Day 1 Visit; catheter-related thrombosis or history of clotting a dialysis access is NOT exclusionary, unless a hereditary coagulopathy has been diagnosed..
9. Treatment with a complement inhibitor (eg, Soliris [eculizumab], Berinert

[C1-INH], Cinryze [C1-INH]), or experimental therapies for the treatment of AMR other than IVIg or rituximab (eg, bortezomib) within 14 days before administration of C1-INH at the Day 1 Visit.
10. Current cancer or a history of cancer within 2 years before providing informed consent, with the exception of successfully treated non-metastatic basal or squamous cell carcinoma of the skin, in situ breast or other in situ lesions considered cured by therapy
11. Any medical condition that, in the opinion of the investigator, might interfere with the subject participation in the study, poses an added risk to the subject, or confounds the assessment of the subject.
12. Female subjects who are pregnant (as evidenced by a positive serum pregnancy test for choriogonadotropin beta at Screening) or breast feeding.
13. Female subject of childbearing potential or male subject not using or not willing to use a medically reliable method of contraception from the first dose of investigational product in any treatment period until 1 month after the last dose of investigational product in the same treatment period.
NOTE: Childbearing potential and the acceptable methods of contraception are defined in Section 7.4.
14. Participation in another interventional clinical study for AMR at Screening; subject may have been withdrawn from an AMR study at any time before Screening.
15. Known or suspected hypersensitivity to the investigational product (ie, C1-INH or placebo), to any excipients of the investigational product, or to any other C1-esterase inhibitor preparation (eg, Berinert) or albumin preparation.
16. Involved in the planning and/or conduct of the study (applies to CSL staff, staff at the study site, and third-party vendors).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-06-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Berinert
Generic name:	Human C1 esterase inhibitor
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-08-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	19-03-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	25-04-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	03-09-2018

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	17-12-2018
Application type:	Amendment
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Approved WMO Date:	10-04-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	04-06-2019
Application type:	Amendment
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Approved WMO Date:	09-07-2019
Application type:	Amendment
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Approved WMO Date:	28-11-2019
Application type:	Amendment
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Approved WMO Date:	16-12-2019

Application type:	Amendment
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Approved WMO Date:	24-12-2019
Application type:	Amendment
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Approved WMO Date:	08-04-2020
Application type:	Amendment
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Approved WMO Date:	16-04-2020
Application type:	Amendment
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Approved WMO Date:	17-04-2020
Application type:	Amendment
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Approved WMO Date:	21-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	15-10-2020

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-01-2021
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
EudraCT	EUCTR2017-000348-17-NL
Other	N/A
CCMO	NL61550.058.17

Study results

Actual enrolment: 4

Summary results
Trial ended prematurely