A partially blinded, prospective, randomized multicenter study evaluating efficacy, safety and tolerability of oral sotrastaurin plus standard or reduced exposure tacrolimus vs. myfortic plus tacrolimus in de novo renal transplant recipients (CAEB071A2214)

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

Summary

ID

NL-OMON34948

Source
ToetsingOnline

Brief title
CAEB071A2214

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym

renal transplantation

Health condition

niertransplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: mycofenolate, renal transplantation, sotrastaurin, tacrolimus

Outcome measures

Primary outcome

Composite efficacy failure (treated BPAR of grade IA or higher, graft loss,

death or lost to follow up) at Month 6 post-transplantation.

Secondary outcome

GFR via MDRD formula, creatinine clearance via Cockcroft-Gault formula, treated

BPAR of grade IA or higher, graft loss, death or lost to follow up >6 months,

adverse events.

Study description

Background summary

Over the past decades, organ allotransplantation has become a common medical procedure with considerable impact on extending and improving the quality of life of patients with end stage renal, cardiac, hepatic or pulmonary failure.
To maximize efficacy and minimize adverse effects, current immunosuppressant (IS) regimens use combinations of IS drugs. Care is taken to achieve synergy or additive immunosuppressive effects via the administration of sub-maximal doses of agents with different mechanism of action while avoiding overlapping

toxicities. Most regimens currently include a regimen of a calcineurin inhibitor (CNI) such as cyclosporine or tacrolimus, together with a lymphocyte proliferation inhibitor such as mycophenolic acid or mycophenolate mofetil. Sotrastaurin (STN) is a novel IS that blocks early T-cell activation via inhibition of protein kinase C (PKC). It is a highly potent and selective inhibitor of the classical (α, β) and novel (δ, *, *, *) PKC isoforms (Ki values range from 0.2 to 3.2nM). The role of PKC isoforms in immune cell signaling is still under intense investigation. At the cellular level, early T-cell activation, but not T-cell proliferation, is strongly inhibited by sotrastaurin as assessed by interleukin-2 (IL-2) secretion.

Study objective

Primary objectives
The primary objective of the study is demonstrate that at least one of the sotrastaurin treatment arms is non-inferior to the active control regimen myfortic + tacrolimus with respect to composite efficacy failure (treated BPAR of grade IA or higher, graft loss, death or lost to follow up) at Month 6 post-transplantation.
Secondary objectives
• Evaluate renal function at Months 6, 12, 24 and 36 post-transplantation using
o Estimated GFR (eGFR) by MDRD formula (eGFRMDRD),
o A composite renal function endpoint defined as eGFRMDRD < 60 mL/min/1.73 m2 at Month 12, or a decrease from Month 3 to Month 12 >= 10 mL/min/1.73 m2 in each sotrastaurin treatment arm relative to the control regimen (Month 12 analysis only),
o Estimated creatinine clearance using the Cockcroft-Gault formula.
• Evaluate the composite efficacy endpoint in the sotrastaurin arms and the control arm at Months 12, 24 and 36 post-transplantation.
• Evaluate individual components (and combinations of the individual components) of the composite efficacy endpoint in the sotrastaurin arms and the control arm at Months 6, 12, 24 and 36 post-transplantation.
• Evaluate safety and tolerability between the sotrastaurin arms and the control arm, including infections, GI tolerability, ECG parameters, and hematological parameters (e.g. neutrophils) at Months 6, 12, 24 and 36 post-transplantation.

Study design

This study is a 3-year, randomized, multicenter, partially blinded, 4-arm study comparing the efficacy and evaluating the safety of oral sotrastaurin + standard or reduced exposure tacrolimus versus the active control myfortic + standard exposure tacrolimus for initial and maintenance prophylaxis of organ rejection in adult de novo renal transplant patients.
Upon meeting inclusion-exclusion criteria, approximately 300 patients (approximately 75 per treatment arm) will be randomized (1:1:1:1) within 24

hours following transplantation. Randomization will be stratified by donor source (living vs. deceased donor) using a
centralized randomization procedure:
• Arm 1: sotrastaurin 100 mg b.i.d. + standard exposure tacrolimus
• Arm 2: sotrastaurin 200 mg b.i.d. + standard exposure tacrolimus
• Arm 3: sotrastaurin 300 mg b.i.d. + reduced exposure tacrolimus
• Arm 4 (control arm): myfortic 720 mg b.i.d. + standard exposure tacrolimus
The daily dose of tacrolimus will be adjusted to maintain target concentrations:
• Standard exposure tacrolimus (whole blood trough levels > 5 - 12 ng/mL)
• Reduced exposure tacrolimus (whole blood trough levels 2 - 5 ng/mL).
The combination of STN + Tac and myfortic + Tac will be considered as study drugs. All patients will receive induction treatment with basiliximab 20 mg on study Day -1 (the day of kidney transplant surgery) and Day 4 (or on the day of discharge if sooner than Day 4) and will receive corticosteroids through Month 36.
• Patients randomized to Arms 1 and 2 will receive blinded sotrastaurin 100 mg b.i.d. or 200 mg b.i.d., plus matching placebo
• Patients randomized to Arm 3 (sotrastaurin + reduced exposure tacrolimus) will receive open-label sotrastaurin 300 mg b.i.d.
• Patients randomized to Arm 4 will receive blinded myfortic 720 mg b.i.d., plus matching placebo.
Data Monitoring Committee.

Intervention

Treatment with sotrastaurin + tacrolimus or standard treatment mycophenolic acid + tacrolimus.

Study burden and risks

Risk: Adverse events of study treatment. Insufficient efficacy of (one of) the experimental treatment arms.
Burden: 21 visits in 3 yearss. All visits: vital signs and blood draws (10-15 ml per visit, 300 ml in total). 11x physical examinations, 21x EKG, 11x pregnancy test (if applicable).
The study burden is not significantly different from regular treatment. Basiliximab infusions (2) are also given during regular care.
Optional PK substudy: not in NL.

Contacts

Public
Novartis

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NL
Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Male or female patients >= 18 years old.
• Recipients of a first or second kidney transplant from a deceased, living unrelated or non-HLA identical living related donor.
• Recipients of a kidney with a cold ischemia time < 30 hours.
• Recipients of a kidney from a donor 10-65 years old.

Exclusion criteria

• Recipients who are unable to receive the first dose of oral study medication within 24 hours after allograft reperfusion.
• Multi-organ transplant recipients.
• Recipients of an organ from an non-heart beating donor.
• Patients receiving a second kidney allograft if the first allograft was functional for less than three years (unless lost due to surgical complication).
• Patients who are treated with drugs that are strong inducers or inhibitors of CYP3A4 at screening and cannot discontinue this treatment.
• Patients with increased cardiac risk: long QT-syndrome or QTcF at baseline exceeding 500

msec, or treatment with drugs inducing QT prolongation, class 1a and class 3 antiarrhythmic drugs, family history of long QT syndrome or of sudden unexplained death, history, in the preceding 3 months of significant and persistent arrhythmias, symptomatic/unstable coronary artery disease requiring hospitalization or a revascularization procedure in the 30 days prior to randomization, chronic heart failure which required hospitalization in the 30 days prior to randomization.
• High immunological risk.

Study design

Design

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

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-09-2010
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Myfortic
Generic name:	sodium mycofenolate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prograft
Generic name:	tacrolimus

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sotrastaurin
Generic name:	Sotrastaurin

Ethics review

Approved WMO Date:	25-03-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	27-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-03-2012
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	clinicaltrials.gov, registratienummer nog niet bekend
EudraCT	EUCTR2009-015456-14-NL
CCMO	NL31865.078.10