A 12-month open-label, randomized, multicenter sequential cohort, dose finding study to evaluate the efficacy, safety and tolerability of oral AEB071 versus Neoral® in combination with Certican®, Simulect®, and corticosteroids in de novo adult renal transplant recipients

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CAEB071A2206 will assess safety, efficacy and target trough levels for optimal dosing of AEB071 combined with Certican in a CNI-free regimen in de novo renal transplant recipients. This study will combine the investigational drug AEB071 with an...

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

Summary

ID

NL-OMON33773

Source
ToetsingOnline

Brief title
AEB071 versus Neoral® in de novo adult renal transplant recipients

Condition

- Other condition

Synonym
rejection, renal transplant

Health condition

orgaanafstoting na niertransplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Het onderzoek wordt gefinancieerd door de opdrachtgever Novartis Pharma B.V.

Intervention

Keyword: open-label, renal, transplant

Outcome measures

Primary outcome

The primary objective of the study is:

- To compare, in Stage 1, the efficacy of AEB071 to that of Neoral, both in

combination with Certican, Simulect, and steroids, at 3 months after

transplantation. Efficacy will be defined using a composite efficacy failure

end point (treated BPAR, graft loss, death or loss to follow-up).

- To compare, in Stage 2, the efficacy of AEB071 regimens with the Neoral

regimen, using a composite efficacy failure endpoint (treated biopsy-proven

acute rejection (treated BPAR), graft loss, death or loss to folow-up).

Secondary outcome

Main secondary efficacy objective:

* compare the composite efficacy failure end point (treated BPAR, graft loss,

death or loss to follow-up) of both AEB071 treatment regimens with the control

regimen (Certican + Neoral) in Month 3, 6 and 12 post transplantation.

Main safety objective:

* compare renal function in the AEB071 treatment arms with the control arm at

Month 3, 6 and 12 post-transplant with calculated GFR using the MDRD formula.

Other secondary objectives:

* Determine the dose or concentration of AEB071 and Certican to be used in

phase III

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 are based on the use of a combination of IS drugs. Care is taken to achieve synergy or additive effects via the administration of sub-optimal doses of agents with different mechanism of action while avoiding overlapping toxicities. Consequently, most regimens are currently based on the use of the combination of a calcineurin inhibitor (CNI) that inhibits T-cell activation, such as Cyclosporin A (CsA, Neoral®) or tacrolimus (FK506, tacrolimus), together with a lymphocyte
proliferation inhibitor such as drugs based on mycophenolic acid (MPA) i.e. CellCept® (mycophenalate mofetil (MMF)); and myfortic® (MPA, as sodium salt, gastro-resistant tablets) or mammalian target of rapamycin (mTOR) inhibitors i.e. Rapamune® (sirolimus, rapamycin) and Certican® (everolimus (RAD001)).
CNIs demonstrate unique immunosuppressive efficacy without major risks of overimmunosuppression, and excellent hematological tolerability. However, their long-term benefit is limited by mechanism-based side-effects, such as renal dysfunction, diabetogenic effects, hypertension, dyslipidemia, and neurotoxicity. The more recently developed IS drugs (MPA; mTOR inhibitors) effectively suppress lymphocyte proliferation, but their combination to CNI-free IS regimen is usually associated with reduced efficacy and increased hematological toxicity, and is therefore not ideal for the majority of transplant recipients. A considerable need remains for safer therapeutic agents inhibiting T-cell activation via a calcineurin-independent mechanism of action.
Mechanism of action Protein Kinase C (PKC) has been shown to play an important

role in T-lymphocyte activation. Among the various PKC isoforms expressed in T cells, PKC * and * play a critical role. Preclinical data showed that by knocking out these isoforms cardiac allograft survival was significantly prolonged in mice and the results confirmed that PKC inhibitors are attractive immunosuppressants by blocking T cell activation via a novel mechanism of action.
AEB071 is a novel small molecular weight immunosuppressant that inhibits PKC-dependent T-cell activation. In contrast to CsA, AEB071 potently and selectively blocks a calcineurinindependent pathway downstream from signal 1 and signal 2 pointing towards a clear differentiation in mode of action between AEB071 and CNIs. AEB071 potently inhibits allogeneic-stimulated T cell proliferation in mixed lymphocyte reaction (MLR) (IC50 = 34 nM in human MLR), but does not exhibit hematological cytotoxicity.

Study objective

CAEB071A2206 will assess safety, efficacy and target trough levels for optimal dosing of AEB071 combined with Certican in a CNI-free regimen in de novo renal transplant recipients. This study will combine the investigational drug AEB071 with an established, effective adjunct therapy (everolimus) to provide a safe entry into the transplant indication and a foundation for the subsequent Phase III pivotal studies. The study will also guide the further development of AEB071 and the selection of an appropriate target range for therapeutic drug monitoring in de novo renal transplant patients.

This study will have 2 stages, with Stage 1 corresponding to phase IIa of drug development (assessment of efficacy) and Stage 2 corresponding to phase IIb (dose finding).

Study design

Each subject will be treated for 1 year. There are 2 treatment arms in Stage 1: twothird of the subjects will be treated with AEB071 (300 mg bid) combined with Certican. onethird of the subjects will be treated with Neoral and Certican. In case 45 patients are included and have been treated for 3 months, an interim analyses will be done to evaluate the efficacy and safety of AEB071. If AEB071 appears to be sufficient safe and effective, 84 new patients will be included in the trial and after 3 months another interim analyses will be done.

In Stage 2, 180 subjects will be included. The dosing has been adapted in Stage 2, based on the results of the interim analyses. After 3 months, an interim analyses will be done.

Intervention

In Stage 1 are 2 treatment groups; twothird of the subjects will receive AEB071

(3 capsules of100 mg bid) in combination with Certican® (target dose of 4-8 ng/mL). Onethird of the subjects will be treated with Neoral® (start dose of 4-8 mg/kg/day) and Certican® (target dose of 4-8 ng/mL).

In Stage 2 are 3 treatment groups; Onethird of the subjects receives AEB071 (3 capsules of 100 mg bid) in combination with Certican® (target dose of 4-8 ng/mL). Onethird of the subjects receives Neoral® (start dose of 4-8 mg/kg/day) and Certican® (target dose of 4-8 ng/mL). Onethird of the subjects receives AEB071 (2 capsules of 100 mg bid) in combination with Certican® (target dose of 8-12 ng/mL).

Study burden and risks

During the transplantation and on day 4 post transplantation, the subject will receive Simulect® via injection.
Furthermore, the subject needs to use corticosteroids to prevent infections.
The corticosteroids will be prescribed by the treating physician.

Treatment: starts after randomisation (AEB071 of Neoral) until end of treatment in Month 12.

Patients will be monitored with help of Physical Examination, blood and urine analyses and ECG at every visit.

A kidney biopsy will be done twice (on the day of the transplantation and on Month 12).

Please refer to section E9 of this form for the nature and extent of the burden and risks associated with participation.

Contacts

Public
Quintiles

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Scientific
Quintiles

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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 and female patients * 18 years old.
* Recipients of a primary kidney transplant from a deceased, living unrelated or non-HLA identical living related donor.
* Recipients of a kidney with a CIT < 24h.
* Recipients of a kidney from a donor 10-65 years old.
* Patients expected to be able to take oral medication within 24h after graft reperfusion.
* Patients willing and capable of giving written informed consent for study participation and able to participate in the study for 12 months.

Exclusion criteria

* Multi-organ transplant recipients or if the patient previously received an organ transplant.
* Recipients of an organ from a non-heart beating donor.
* Patients who are recipients of A-B-O incompatible transplants, all CDC cross-match positive transplants.
* Patients without functional graft 24h after graft reperfusion (functional graft being defined as urine output of more than 250 mL/12h for patients without residual urinary output from native kidneys, or as a decrease in serum creatinine by at least 20% from pre-transplant).
* Patients with a platelet count < 100,000/mm3 at screening.
* Patients with an absolute neutrophil count of < 1,500/mm³ at baseline before surgery or WBC count of < 2,500/mm³.
* Patients who are treated with drugs that are strong inducers or inhibitors of CYP3A4 at screening and who can not discontinue this treatment (see Appendix 3).
* Patients with QTc > 500 ms, long QT syndrome (own or with a family history) or with a family history of sudden unexplained death.
* Patients with LBBB or who experienced, during the previous 6 months, hospitalisation for heart failure of cardiac etiology, or significant and persistant left-ventricular dysfunction

(LVEF < 40%).
* Patients with a history, in the preceeding 3 months, of significant and persistent arrhythmias such as ventricular fibrillation or tachycardia, or atrial fibrillation or flutter.
* Patients requiring antiarrhythmic drugs with QT-prolonging properties (such as amiodarone, sotalol, dofetilide, quinidine, procainamide, disopyramide).
* Patients with symptomatic coronary artery disease.
* Use of other investigational drugs or a non-protocol immunosuppressant, including induction agents other than Simulect, at randomization, or within 30 days or 5 half-lives prior to randomization, whichever is longer.
* History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures.
* Patients who are anti-HIV-positive, or HBsAg-positive. Anti-HCV positive patients are excluded, except patients with negative PCR-result. Laboratory results obtained more than 6 months prior to study entry should be repeated within the first week after randomization. Patients who test positive for any of the viral indicators after randomization will be discontinued from study treatment.
* Recipients of a kidney from a donor who tests positive for HIV, HBsAg or anti-HCV.
* Sensitized patients (most recent anti-HLA class I Panel Reactive Antibodies (PRA) > 20% by a CDC-based assay or > 50% by a flow cytometry or ELISA-based assay) or patients identified otherwise to be at high immunological risk.
* History of malignancy of any organ system, treated or untreated, within the past 5 years regardless of evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin (excised * 2 years prior to randomization).
* Patients with severe systemic infections, current or within the 2 weeks prior to randomization.
* Patients with any history of significant coagulopathy or medical condition requiring long-term systemic anticoagulation after transplantation, which would interfere with obtaining biopsies. Low dose aspirin treatment (up to 200 mg/day) is allowed. (Plavix® is not allowed).
* Evidence of severe liver disease, including abnormal liver profile (AST, ALT or total bilirubin > 3 times ULN) at screening.
* Patients with BMI > 30.
* Patients who have severe hypercholesterolemia (> 350 mg/dL; > 9 mmol/L) or hypertriglyceridemia (> 500 mg/dL; > 8.5 mmol/L). Patients with controlled hyperlipidemia are acceptable.
* Patients with any condition which is expected to prohibit full-dose Certican or Neoral therapy, as per current product labels.
* Patients with any surgical or medical condition, which in the opinion of the investigator, precludes enrollment in this trial.
* Patients who are unlikely to comply with the study requirements or unable to cooperate or communicate with the investigator.
* Pregnant or nursing (lactating) women, and women who might become pregnant during the study.

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):	23-01-2008
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	na
Generic name:	AEB071 drug substance mono acetate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Neoral®
Generic name:	Ciclosporine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	AEB071 drug substantie mono-acetaat
Product type:	Medicine
Brand name:	Simulect®
Generic name:	Basiliximab

Registration:	Yes - NL intended use

Ethics review

Approved WMO Application type:	First submission
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
EudraCT	EUCTR2006-004540-23-NL
ClinicalTrials.gov	NCT00504543
CCMO	NL18064.078.07