An extension to a 12-month, open-label, randomised, 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

Published: 26-09-2008
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The purpose of this extension is to provide continued treatment and to assess the long term safety, efficacy and tolerability of oral AEB071 plus Certican® vs. Neoral® plus Certican® in de novo renal transplant recipients. The study is a…

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

Summary

ID

NL-OMON37034

Source
ToetsingOnline

Brief title
CAEB071A2206-E1

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 door de opdrachtgever/sponsor Novartis Pharma B.V. gefinancieerd.

Intervention

Keyword: open-label, renal, transplant

Outcome measures

Primary outcome

To characterise the general and renal-specific glomerular filtration rate (GFR)

(MDRD) safety profile, up to 60 months post transplantation, of renal

transplant patients treated with AEB071 in combination with Certican® (CNI

free) versus a standard CNI-based regimen.

Secondary outcome

To characterise the efficacy profile, composite endpoint of BPAR > IA, graft

loss, death, or lost to follow up, up to 48 months post transplantation, of

renal transplant patients treated with AEB071 in combination with Certican®

(CNI free) versus a standard CNI-based regimen.

Collection of efficacy data. The key efficacy parameter is the incidence over

42 months of the composite endpoint of BPAR >= 1A, graft loss, death, or lost to

follow-up in the two study arms.

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 α 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

The purpose of this extension is to provide continued treatment and to assess the long term safety, efficacy and tolerability of oral AEB071 plus Certican® vs. Neoral® plus Certican® in de novo renal transplant recipients.
The study is a continuation of a CNI-free core study. The extension will allow continued access to AEB071 after the end of the core study to patients who were on study treatment at the end of the core study and may provide early notification of safety signals on AEB071 in patients during the 48 months extension study period.

Study design

See protocol page 24 and 15 (Study design).

Intervention

There are two treatment groups: 2/3 of the patients will be treated for 3 years* with AEB071 (3 capsules of 100 mg bid) in combination with Certican® (4 tablets of 0,75 mg bid). 1/3 of the patients will be treated for 3 years*with Neoral® (starting dose of 4 mg/kg/day capsule) and Certican® (2 tablets of 0,75 mg bid).

*CAEB071A2206: 1 year treatment, CAEB071A2206E1: 2,5-5 year treatment

Study burden and risks

The patient will have to use corticosteroids to resist infections.
Cortocosteroids will be prescibed by the investigator.

Treatment: after completion of all visits in the core study, treatment will be continued for 48 months in the extension study.

Patients will be examined during the study: physical examination, blood and urine tests. Besides, an ECG will be performed by the patient 9x during the extension study.

Contacts

Public
Novartis

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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

•The patient has given written informed consent to participate in the extension study.
•The patient has been maintained on AEB071/Certican® or Neoral®/Certican®, consistent with their original randomisation, at their core study Month 12 visit.
•Women capable of becoming pregnant are required to practice a medically approved method of birth control as long as they are on study medication and for a period of 3 months following discontinuation of study drug(s).

Exclusion criteria

•Inability or unwillingness to comply with the immunosuppressive regimen or the protocol.
•Pregnancy.

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):	21-07-2009
Enrollment:	25
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:	NA
Generic name:	AEB071 drug substance mono acetate
Product type:	Medicine
Brand name:	Neoral®
Generic name:	Ciclosporine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	26-09-2008
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-06-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	06-10-2010
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:	18-01-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-03-2011
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:	07-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	07-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2012
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:	11-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2012
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
EudraCT	EUCTR2008-000531-18-NL
ClinicalTrials.gov	NCT00820911
CCMO	NL24852.078.08