A Three-Part, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Sequential Adaptive, Phase II Study to Evaluate the Safety, Tolerability and Efficacy of OPN305, a Humanised Monoclonal Antibody that Blocks Toll-Like Receptor 2, in Renal Transplant Patients at High Risk of Delayed Graft Function

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Primary Objectives:*Phase 0: To determine the receptor occupancy of OPN-305 1.5mg/kg in patients receiving an ECD, DCD or SCD(CIT>18h) kidney transplantation and to verify the doses of OPN-305 to be used in Part A of the study.*Part A: to select…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON39887

Source
ToetsingOnline

Brief title
OPN305 to prevent Delayed Graft Function in kidney transplantation.

Condition

- Renal and urinary tract therapeutic procedures

Synonym
delayed graft function in kidneytransplant

Research involving
Human

Sponsors and support

Primary sponsor: Opsona Therapeutics Ltd
Source(s) of monetary or material Support: industry and European Union (FP7)

Intervention

Keyword: Delayed Graft Function, humanised IgG4 monoclonal antibody, Renal Transplant

Outcome measures

Primary outcome

Primary Endpoints:

Phase 0:

TLR2 receptor occupancy

Part A:

Incidence of dDGF

Parts A and B: (including patients from Part A on the selected OPN-305 dose

and placebo as described above).

*Incidence of dDGF; defined as the need to initiated dialysis in the first 7

days following renal transplantation (dDGF).

Note: Dialysis to control biochemical parameters such as isolated rises in potassium or fluid overload will be assessed by the DSMB and a secondary endpoint will be DGF (the need for dialysis within 7 days) excluding these patients. Participating study sites are advised to consider using conventional means of reducing the serum levels before resorting to dialysis if these fail.

Secondary outcome

Secondary Endpoints for Part A.

*dDGF excluding dialysis for hyperkalaemia or hypervolaemia only (based on the DSMB adjudication).

*fDGF

*Duration of maximal TLR2 receptor occupancy

*PK

Secondary Efficacy Endpoints (Parts A and B)

These endpoints are ranked in order of importance with regard to efficacy assessment:

1. Serum creatinine and Iohexol clearance at 7 days and 6 months

2.Components of the composite endpoint:

a.Incidence of biopsy-proven kidney allograft rejection (biopsies will be done on a for-cause basis only).

b.Graft loss

c. Report of patient death(s)

d. Patients lost to follow up

Note: the components of this composite endpoint will be combined with the graft

function in a seperate analysis.

3.Time to biopsy-proven kidney allograft rejection (biopsies will be done on a for-cause basis only).

4. Functional DGF (fDGF) in patients who do NOT recieve dialysis in the first 7days post-transplantation. fDGF is defined as failure to reduce serum creatinine by at least 10% per day during 3 consecutive days in the first 7days following transplant surgery.

5.Time to first dialysis and DGF duration. DGF Duration is defined as;

a.For dDGF, it is the time from the end of the transplantation surgery until completion of the final dialysis for DGF

b.For fDGF, it is the time from transplantation to the time when creatinine starts to fall by at least >10% without dialysis

6. Incidence of the initiation of dialysis between 7 and 30 days post-transplantation.

7. Rate of primary non-function (permanent lack of function of the allograft).

8. Blood and urine biomarkers for acute kidney injury (AKI)

9.Duration of initial hospitalisation and the duration and reasons for hospital re-admissions.

Pharmacokinetic (PK) & Pharmacodynamic (PD) Endpoints (Phase 0, Parts A and/or B)

PK variables will include Cmax, Tmax, t and AUC * all patients in Phase 0 and up to 12 patients in each dose-group in Part A

*Immunogenicity of OPN305 (re-establishment of the screening cut-points for

anti-drug antibodies [ADA] and confirmatory cut-point of ADA) * Phase 0

*Immunogenicity of OPN305 (binding and neutralising antibodies) * Parts A and B

*Effect of OPN305 on pro-inflammatory cytokines * Phase 0 and Part A

*Extent and duration of TLR2 receptor occupancy on monocytes by OPN305 * Phase

0 and Part A

*Serum amyloid A (SAA) as a marker of acute inflammation * Phase 0 and Part A

*Secreted Phosphoprotein 1 (SPP-1) and Tissue Inhibitor Metallo-Protease 1

(TIMP-1) RNA as markers of acute inflammation * Part A

Study description

Background summary

OPN305 is a humanised IgG4 monoclonal antibody (MAb) against Toll-like receptor 2 (TLR2) that has orphan medicinal product designation from the European Medicines Agency (EMA) for prevention of Delayed Graft Function (DGF) following solid organ transplantation. A similar designation has been granted by the Food & Drug Administration in the USA in December 2011. DGF, for this study, is defined as the post-operative failure of a transplanted kidney that requires dialysis in the 7 days following transplantation. DGF management increases the associated health-economic costs.
DGF in the first week following transplantation has been associated with a higher risk of graft loss at 1 year. OPN305 may reduce the rate of DGF by reducing the innate immune response following ischaemic-reperfusion (I-R) injury of the donor graft. The inhibitory effect of the anti-TLR2 antibody OPN305 on inflammatory signals resulting from I-R injury has been proven in murine and porcine model studies. Moreover, the anti-inflammatory properties of OPN305, in combination with immunosuppressive drugs, may contribute directly to the reduction of allograft loss. Therefore, OPN305 may have promise as a new treatment for renal allograft recipients as it may reduce post-transplant Acute Tubular Necrosis (ATN), control inflammation caused by I-R injury in the transplanted organ and help prevent allograft rejection by an accessory immunosuppressive effect.
A randomised, double-blind, placebo-controlled, dose-escalating Phase I study to assess the safety and tolerability of single ascending IV doses of OPN 305 in healthy subjects has been completed, Forty-one male subjects were enrolled in this study; 29 received one IV dose of OPN305 and 12 received placebo. The

most frequently reported adverse events (AE) in subjects receiving OPN305 were nasopharyngitis, headache, abdominal pain and dizziness. No dose relationship was apparent for the incidence of these AEs. There were no severe or fatal AEs reported.
Two placebo subjects reported 3 serious AEs; one subject experienced a cerebrovascular accident and carotid artery dissection and another suffered a ligament rupture.
Pharmacokinetic and pharmacodynamic data have shown:
*Up to 100% TLR2 receptor occupancy for *14 days has been achieved at all dosages tested
*The ex vivo whole blood assays demonstrated inhibition of IL-6 stimulation release following ex vivo stimulation by TLR2 agonists after OPN-305 administration
*The pharmacokinetics of OPN305 are proportional to dose
*No neutralising antibodies have been detected

Study objective

Primary Objectives:

*Phase 0: To determine the receptor occupancy of OPN-305 1.5mg/kg in patients receiving an ECD, DCD or SCD(CIT>18h) kidney transplantation and to verify the doses of OPN-305 to be used in Part A of the study.

*Part A: to select the optimal single IV dose of OPN-305 for Part B of the study in ECD/DCD/SCD(CIT>18h) kidney transplantation patients. The primary endpoint for this objective is:
o The incidence of DGF on Day 7 defined as the need to initiate dialysis in the first 7 days post-transplantation (dDGF) in patients receiving an ECD/DCD/SCD(CIT>18h) kidney transplantation
Secondary endpoints that will contribute to the decision will be:
o Functional DGF, defined as a failure of the serum creatinine to decrease by at least 10% daily on 3 successive days during the first week post transplantation (fDGF). This endpoint applies only to patients who do NOT receive dialysis in the first 7 days post-transplantation. A creatinine decrease in patients receiving dialysis can be an outcome of dialysis and not an indicator for the absence of fDGF.
o Receptor occupancy.

*Part B: to extend the evaluation whether the optimal dose of OPN-305 from Part A can reduce the incidence of DGF
*Parts A and B: to evaluate whether OPN-305 can reduce the incidence of DGF defined as the initiation of dialysis in the first 7 days following transplantation (dDGF)

Secondary Objectives (Phase 0)
To determine the pharmacokinetics and safety of a single-dose IV administration

of OPN-305 1.5mg/kg

Secondary Objectives (Part A only)
*To assess the safety and pharmacokinetics of different doses of OPN305 in patients undergoing ECD/DCD/SCD(CIT>18h) kidney transplantation.

Secondary Objectives (data from Parts A and B Combined)
To assess the effect in patients receiving an ECD, DCD or SCD(CIT>18h) kidney transplantation of single IV doses of OPN-305 on:
*Graft function
*Composite endpoint
o Graft loss
o Incidence of biopsy-proven kidney allograft rejection (biopsies will be done on a for-cause basis only)
o Patient death
o Lost to follow-up*Functional DGF (fDGF) in patients who do not receive dialysis in the first 7 days following transplantation
*Time to biopsy-proven kidney allograft rejection (biopsies will be done on a for-cause basis only)
*Functional DGF (fDGF) in patients who do not receive dialysis in the first 7 days following transplantation
*Time to first dialysis and DGF duration. DGF Duration is defined as;
o For dDGF, it is the time from the end of the transplantation surgery until completion of the final dialysis for DGF
o For fDGF, it is the time from transplantation to the time when creatinine starts to fall by >10% without dialysis
*Incidence of dialysis between Days7 and 30.
*Incidence of primary non-function.
*Blood and urine biomarkers for acute kidney injury (AKI)
*Duration of initial hospitalisation and the duration and reason for subsequent hospital re-admissions
*Safety
- Incidence of infections by type and actual organism.

Study design

This is a three-part, group sequential, adaptive, Phase II study to assess the safety and to evaluate the clinical effect of single intravenous doses of OPN305 on renal function in patients scheduled to receive a kidney transplantation from:

*An extended criteria donor (ECD) (subject to a limit of 50% of all patients in Parts A and B) defined as:
o Donor *60 years of age
o Donor 50-59 years of age with all three of the following criteria present:
-Death due to cerebrovascular accident
-Pre-existing history of systemic hypertension

-Terminal serum creatinine *1.5mg/dL (132.6µmol/L)

OR
*Donation after circulatory death (DCD) - previously *Donation after Cardiac Death* and *Non Heart Beating Donors*

OR
*A standard criteria donor (SCD) with a cold ischaemic time (CIT) greater than 18 hours at randomisation in Parts A and B (SCD[CIT>18h])

Note 1: SCD Definition; An SCD donor is;
*Any donor <50 years of age who is not a DCD and has a serum creatinine <2mg/dL (176.9µmol/L)
*Any donor 50-59 years of age who has none or only one of the following criteria (hypertension, cerebro-vascular accident [CVA] or creatinine >1.5mg/dL but < 2mg/dL), i.e.: none or only one of the following;
oAged 50-59 with a creatinine <2mg/dL (176.9µmol/L) who has no history of hypertension and died for reasons other than a CVA;
OR
oAged 50-59 who died due to a CVA with creatinine <1.5mg/dL (132.6µmol/L) and no history of hypertension;
OR
oAged 50-59 with a history of hypertension who died for reasons other than CVA (e.g., brain trauma)and creatinine < 1.5mg/dL (132.6µmol/L)

Note 2: Maximum CIT for all Donor kidney types: The patient should not be randomised if the CIT time for any kidney is expected to be greater than 30h at the start of surgery. If the patient is randomised and there are unforeseen delays at the time of surgery an additional 2 hours CIT will be permitted. If the CIT at the outset of surgery is more than 32 hours the patient should not be dosed with OPN-305/placebo. The start time for measurement of CIT is the time of clamping of the donor kidney.

Prior to the initiation of the double-blind, randomised study an open-label, single arm, pilot (Phase 0) pharmacokinetic/pharmacodynamic (PK/PD) evaluation of single-dose intravenous (IV) pharmacokinetic variables over 28 days, receptor occupancy (RO) over 14 days and safety over 28 days following a single IV dose of open-label OPN-305 1.5mg/kg in 8 patients was done.

The data generated in Phase 0 were used to select the doses of OPN-305 for Part A of the double-blind, randomised study: OPN-305 0.5, 1.5 and 5mg/kg IV.

The data from patients in Phase 0 will not be used in the main Phase II study.

Intervention

Part A:
This will be a single-infusion, dose-confirmation part of the study to determine the optimal IV dose to be studied further in Part B. The rationale is to confirm whether there is a difference in dose required should receptor upregulation require a higher dose for the same occupancy period and to assess if there is a trend to better efficacy based on the primary endpoint. Three IV doses of OPN305 will be compared to IV placebo and will be randomised 1:1:1:1. An independent Data and Safety Monitoring Board (DSMB) will assess safety, review the PK/PD and efficacy data from Part A, and decide on the optimal dose to be used in Part B.
Patients who give written informed consent will be screened for eligibility and randomised to one of the treatment groups. The treatment arms in Part A will be as follows:
*OPN-305 0.5, 1.5 or 5.0mg/kg
AND
*Matching placebo

There will be 144 patients randomised in Part A; 36 patients in each of the 4 dose groups.
At the end of Part A, the DSMB will decide which active dose to use in Part B based on a review of safety, PK/PD and efficacy data. In the event that it is not possible to distinguish between the doses, the lowest effective dose will be selected. At the end of Part A also, the assumptions for the primary endpoint will be reassessed and a sample re-estimation, based on conditional power, may be required. A decision on futility will also be made at this time.

Part B: The single IV dose chosen by the DSMB from Part A will be used in Part B to further assess the effect of OPN305 on DGF versus placebo in the first 7 post-operative days in patients undergoing ECD/DCD/SCD(CIT>18h) kidney transplantation. The primary endpoint will be the proportion of patients who require dialysis during this time. The sample size for the combined optimal dose in Part A plus Part B is based on a superiority design (OPN305 versus Placebo). Data from patients in Part A who received the dose of OPN305 used in Part B as well as the placebo patients from Part A and all of the patients from Part B will therefore make up the efficacy analysis database for the study.
126 Patients will be randomised in a double-blind manner in Part B; 63 patients will be randomised to a single IV dose of OPN305 and 63 to placebo. Therefore, a total of 270 patients will be enrolled into the double-blind parts of the study (144 in Part A and 126 in Part B).

Study burden and risks

NA

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

Inclusion Criteria for Transplant Recipients: ;Adult patients receiving an ECD, DCD, or an SCD (CIT>18h at randomisation) kidney transplantation satisfying the following:;*Provide written informed consent
*Accepted for renal transplantation due to end stage renal disease
*First or second renal transplant recipient. For second renal transplantations:
- the second transplant should NOT be due to rejection.
- Panel reactive Antibody (PRA) should be <10%
- Minimum 3 months since the loss of the first transplanted kidney.;*Recipient of a kidney meeting the inclusion criteria for a donor kidney
*At least 18 years of age
*If sexually active female, patient must be/have one of the following:
- Post-menopausal defined as the absence of menses for at least one year (serum FSH

*20IU/L can also be measured according to local practice), OR
- Surgically sterile defined as a bilateral tubal ligation at least 6 months prior to administration of study drug, bilateral oophorectomy, or complete hysterectomy, OR
- Using an effective means of contraception (per protocol appendix 1 that is planned to continue for the duration of the study (6 months), AND
- Negative urine pregnancy test if the patient is capable of providing a urine sample (serum *-HCG will be confirmed as part of screening biochemistry) in the 48 hours before OPN305 administration.
Female patients of childbearing potential who are anuric must have a serum pregnancy test. If the result of that test is not, or will not be available before the start of the study-drug administration then the Investigators must ensure, to the best of their knowledge, that the patient is not or could not be pregnant. The result of the serum pregnancy test should be recorded as soon as possible.;*If sexually active male, patient must
- Agree to use an effective means of contraception (per site-specific guidelines) that is planned to continue for the duration of the study (6 months)
- Agree not to donate sperm until 6 months after dosing;*Dialysis-dependent (including peritoneal dialysis) at the time of transplantation as documented by:
- Requirement for at least 2 dialysis sessions/week in the 56 days before transplantation;*Willingness to comply with the protocol procedures for the duration of the study, including scheduled follow-up visits and examinations ;Inclusion Criteria for Donor Kidney:
*The donor kidney must be considered compatible according to local transplant guidelines
*A donor kidney from one of the following categories;
- Donation after Circulatory Death (only classification Maastricht 3)
- Extended Criteria Donor (to a maximum of 50% of patients in each dose- or placebo-group in Parts A and B) defined as:
*Donor *60 years of age
*Donor 50-59 years of age with all three of the following criteria present:
+Death due to cerebrovascular accident
+Pre-existing history of systemic hypertension
+Terminal creatinine * 1.5mg/dL (132,6µmol/L)
-Standard Criteria Donor with a cold ischaemic time >18 hours at time randomisation in Parts A and B.
*Kidney allograft maintained in cold storage with or without machine perfusion

Exclusion criteria

Exclusion Criteria for Transplant Recipients:;*Use of an investigational drug in the 30 days before surgery
*Participation in any other research study (drug or non-drug) without prior approval from the Medical Monitor
*Known hypersensitivity to human monoclonal antibodies or any of the study-drug excipients
*Previous hypersensitivity to basiliximab and anti-thymocyte globulin (ATG) if induction with one of these agents would normally be required
*Pre-operative serum potassium >6.0mmol/L

oNote: Dialysis before surgery to correct hyperkalaemia or hypervolaemia is recommended
*History or known HIV or HBV (surface antigens) positive
oNote: Patients known to have a positive virology history but current unknown status must be assumed to be still positive at screening. Patients with a positive history who are confirmed to be sero-negative at screening may enter the study.
*History of malignancy within the last five years judged to be at risk of relapse within the timeframe of the clinical trial, except excised squamous or basal cell carcinoma of the skin or cervical intraepithelial neoplasia
*Scheduled to undergo multi-organ transplantation
*Planned dual kidney transplantation
*Presence of clinically significant infections requiring continued therapy
*Active tuberculosis
*Existence of any surgical or medical condition, other than the current transplantation which, in the opinion of the investigator, might significantly alter the distribution, metabolism or excretion of study medication
*Presence of uncontrolled diabetes mellitus (defined according to local diagnostic procedures)
*Current drug and/or alcohol abuse
*History or presence of a medical condition or disease that in the investigator's assessment would place the patient at an unacceptable risk for study participation
*Lactating or pregnant woman
*Patient institutionalised by administrative or court order;Exclusion Criteria for Donor Kidney:
*Expected CIT >30h for any kidney type at the start of surgery
oNote: If the patient is randomised and there are unforeseen delays at the time of surgery an additional 2 hours will be allowed. If the CIT at the outset of surgery is more than 32 hours the patient should not be dosed with OPN-305/placebo. The start time for measurement of CIT is the time of clamping of the donor kidney.
*Terminal creatinine > 2mg/dl (176.9µm/L) (ECD>1.5mg/dl [132.6µmol/L])
*Donor who is known to have received an investigational drug for I-R injury or graft rejection (immunosuppressant) in the 48h before organ recovery
*Participation in any other research study (drug or non-drug) without prior approval from the Medical Monitor
*Kidney donor <5 years of age or <20kg body weight
*Living donor allograft
*HLA antibody or ABO antibody incompatible kidney defined as a positive cytotoxic crossmatch
*Donor institutionalised by administrative or court order if forbidden by local laws or regulations

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-09-2013
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Humanised IgG4 Monoclonal Antibody against Toll-like receptor 2 (sub33114)

Ethics review

Approved WMO Date:	19-11-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-03-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2013
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-10-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012-001455-39-NL
CCMO	NL41764.042.12