A randomized double-blind placebo-controlled study to evaluate the efficacy and safety of Cinryze® (C1 esterase inhibitor [human]) for the treatment of acute antibody-mediated rejection in kidney transplant patients

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To evaluate the efficacy of Cinryze administered with plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free intravenous immunoglobulin (IVIg) for the treatment of acute antibody-mediated rejection (AMR) of renal allograft...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON44758

Source
ToetsingOnline

Brief title
SHP616-302

Condition

- Renal disorders (excl nephropathies)

Synonym
kidney transplant

Research involving
Human

Sponsors and support

Primary sponsor: Shire
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: acute antibody-mediated rejection, Cinryze, kidney transplant

Outcome measures

Primary outcome

Primary Efficacy Endpoint: Proportion of subjects with new or worsening TG at 6

months after treatment initiation as determined by Banff criteria

Secondary outcome

Key Secondary Efficacy Endpoint: Proportion of subjects with all-cause graft

failure (ie, return to

permanent dialysis and/or removal of the transplanted kidney and/or clinical

determination of cessation of

graft function in any subject that had received a pre-emptive kidney transplant

prior to starting dialysis) at 4 years following treatment of the initial

qualifying AMR episode

Secondary objectives from study entry to 6 months:

- To assess renal function

- To assess proteinuria

- To assess change in histopathology

- To assess graft outcomes

Secondary objectives from study entry to 4 years:

- To assess renal function

- To assess proteinuria

- To assess graft outcomes

- To assess resolution of AMR

- To assess safety and tolerability of CINRYZE in kidney transplant

- To assess subject survival status

Study description

Background summary

Since AMR results in complement-mediated damage to a transplant, the sponsor hypothesized that a complement inhibitor such as plasma-derived C1 inhibitor (C1 INH) could effectively protect a renal allograft while reduction of DSA is achieved with standard-of care plasmapheresis, plasma exchange, or immune adsorption treatments with sucrose-free IVIg, resulting in less long-term damage to the kidney and prolonged graft survival. For more information please refer to the rationale in the protocol.

Study objective

To evaluate the efficacy of Cinryze administered with plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free intravenous immunoglobulin (IVIg) for the treatment of acute antibody-mediated rejection (AMR) of renal allograft in kidney transplant recipients as measured by the proportion of subjects with new or worsening transplant glomerulopathy (TG) at 6 months after treatment initiation.

Study design

This randomized, double-blind, placebo-controlled multicenter, multinational study will assess the efficacy and safety of CINRYZE with protocol-mandated DSA reduction treatment and sucrose-free IVIg for the treatment of acute AMR in kidney transplant recipients. Eligible study
subjects will have had a kidney transplant with adequate function defined as having a pre-AMR baseline eGFRMDRD >=20 mL/min/1.72m2 if the qualifying AMR episode occurs <=21 days after transplant or pre-AMR baseline eGFRMDRD >=30

mL/min/1.72m2 if the qualifying AMR episode
occurs >21 days after transplant. The pre-AMR baseline is the highest eGFRMDRD value obtained following the kidney transplant and within 30 days prior to the qualifying AMR episode. If more than 1 eGFRMDRD value is available, a mean of the 2 highest values (at least 1 day apart and both prior to the AMR episode) will be used as the pre-AMR baseline value. If no eGFRMDRD was obtained within 30 days prior to the qualifying AMR episode, it can be evaluated within a 60-day period.

After the screening period, approximately 112 eligible subjects with biopsy-proven AMR will be randomized (56 per treatment arm) to receive either IV Cinryze or placebo in a 1:1 ratio. Treatment will last 25 days and follow-up period up to 48 months.

Intervention

Cinryze: an initial intravenous (IV) infusion of 5000 U Cinryze on Day 1, followed by 2500 U of Cinryze IV on Days 3, 5, 7, 9, 11, and 13

Placebo (0.9% sodium chloride for infusion): an IV infusion on Days 1, 3, 5, 7, 9, 11, and 13 (100 mL)

Study burden and risks

For the study patients will have following procedures:
-physical examination: 2x*
-research lower extremities: 8x*
- ECG: 2x
-pregnancy test: 2x*
-blood sampling: zie E6.
-kidney biopsy: 2x*
-questionnaire: 11x
*in case of a second AMR, subjects eligible for retreatment will complete a subset of the screening procedures.

CINRYZE® is prepared from human blood supplies and therefore it may contain disease causing viruses (for example: the viruses of hepatitis C and HIV and mad cow disease or Creutzfeldt-Jakob disease [CJD agent]). The risk that CINRYZE® may transmit viruses has been addressed by screening blood donors, by testing donated blood, and by removing certain viruses through heat and filtration during the manufacturing process. These combined procedures make the risk of transmission of viruses very limited.
The active ingredient in CINRYZE® is a protein that may cause abnormal blood clotting (thrombus).
Headache, upper respiratory tract infections (chest cold) and sinusitis (stuffy nose), high blood sugar levels, burning in the vein, hot flush, cough, nausea,

vomiting, diarrhea, abdominal pain, joint swelling, joint pain, muscle pain, fever have also been reported in association with the intravenous use of CINRYZE®.

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.Be >= 18 and <=70 years of age.
2.Weigh >=45 kg with a body mass index (BMI) <35 kg/m2 at screening.
3.Have HLA DSA identified at the time of diagnosis of AMR. If it is anticipated that the local DSA results will not be available within the screening period, previously obtained local DSA results can be used to assess eligibility, if obtained after kidney transplant and within 30 days prior to the qualifying AMR episode. In any instance, a local DSA test should still be performed at the time of AMR diagnosis.

4.Have a first qualifying episode of AMR in the subject's current renal allograft between 72 hours and 12 months after transplant defined by a renal allograft biopsy demonstrating neutrophil and/or monocyte infiltration in the peritubular capillaries and/or glomeruli with or without evidence of C4d by immunohistopathology according to 2013 Banff criteria for AMR.
5.Have achieved adequate renal function defined as: Pre-AMR baseline eGFRMDRD >=20 mL/min/1.73m2 for a qualifying AMR episode occurring <=21 days after transplant or pre-AMR baseline eGFRMDRD >=30 mL/min/1.73m2 for a qualifying AMR episode occurring >21 days after
transplant. The pre-AMR baseline is the highest eGFRMDRD value obtained following the kidney transplant and within 30 days prior to the qualifying AMR episode. If more than one eGFRMDRD value is available, a mean of the 2 highest values (at least 1 day apart and both prior to the
AMR episode) will be used as the pre-AMR baseline value. If no eGFRMDRD was obtained within 30 days prior to biopsy, it can be evaluated within a 60 day period.
6.Receive first dose of investigational product at least 7 days after kidney transplant and within 7 days after the qualifying renal allograft biopsy procedure that was positive for AMR.
7.Be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.
8.If female and of child-bearing potential, have a negative urine pregnancy test confirmed by a negative serum beta human chorionic gonadotropin pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Day 1 visit.
9.Agree to comply with any applicable contraceptive requirements of the protocol.

Exclusion criteria

1.Have received pediatric en bloc kidney transplant.
2.Have primary Focal Segmental Glomerulosclerosis, rapidly progressive glomerulonephritis,membrano-proliferative glomerulonephritis type 1 (including C3 Glomerulopathy), "dense deposit disease", or Thrombotic microangiopathy as the cause of native kidney failure.
3.Have prior or concurrent non-renal solid organ transplant or hematopoietic stem cell transplant (HSCT) or have more than 2 completed kidney transplant procedures (note: 1 double kidney transplant procedure is considered to be 1 procedure).
4.Have a known neoplastic lesion in the transplanted allograft.
5.Have, any ongoing infection that causes hemodynamic compromise or as determined by the investigator and/or medical monitor, any surgical or medical condition that could interfere with the administration of investigational product, interpretation of study results, or could compromise patient safety, including (as determined by the transplanting surgeon and documented in the operative report) any major technical complications of the renal artery, renal vein, or ureteral anastomosis.
6.Have ongoing treatment for hepatitits C virus (HCV) infection.
7.Have had a myocardial infarction (MI) within the past 6 months and/or at the time of screening are treated with anticoagulants and/or antiplatelet agents (excluding asprin) for a previous myocardial infarction.
8.Have a history of abnormal bleeding, clotting events or disorders (excluding a history of

clotted hemodialysis access or superficial thrombophlebitis in the absence of medically-confirmed coagulopathy), any coagulopathy (docuemented or clinically suspected). For example, patients should be excluded if they have a history of renal allograft arterial or venous thrombosis, deep vein thrombosis, pulmonary embolism, ischemic cerebrovasculara accident (stroke) or transient ischemic attack (TIA), any large vessel thrmobosis..
9.Have a history of allergic reaction to CINRYZE or other blood products.
10.Have had any change in androgen therapy (eg, danazol, oxandrolone, stanozolol, testosterone), tranexamic acid, epsilon-aminocaproic acid, or other fibrinolytics within 3 months before the first dose of investigational product.
11.Have participated in the active dosing phase of any other investigational drug study within 30 days prior to dosing with investigational product.
12.Have any of the following local laboratory values reported prior to dosing with investigational product:
Within 24 hours prior to subject dosing, white blood cell count <0.5×10^9/L or >20×10^9/L (the value of >20 x 10^9/L should be excluded if obtained during steroid treatment)
Within 24 hours prior to dosing , platelet count <25×10^9/L or >600×10^9/L
13. Be pregnant or breastfeeding.
14. Have received any of the following agents within 1 month prior to the first dose of investigational product:
Sucrose-containing IVIg
Any C1 INH (plasma-derived [eg, CINRYZE®, Berinert®, Cetor®] or recombinant [eg, Rhucin®])
Eculizumab (Soliris®)
Ecallantide (Kalbitor®)

Study design

Design

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

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	19-03-2017
Enrollment:	7
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	28-09-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-05-2019
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	EUCTR2015-000726-11-NL
CCMO	NL53808.078.15

Study results

Results posted: 27-05-2020

First publication
01-01-1900