A controlled, open-label post-authorisation efficacy and safety study in imlifidase desensitised kidney transplant patients with positive crossmatch against a deceased donor prior to imlifidase treatment, including non-comparative registry and concurrent reference cohorts

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This study has been transitioned to CTIS with ID 2024-511810-18-00 check the CTIS register for the current data. Primary objective• To determine the 1-year graft failure-free survival in highly sensitised kidney transplant patients, pre-treated with...

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

Summary

ID

NL-OMON55984

Source
ToetsingOnline

Brief title
Efficacy and safety of imlifidase in kidney transplant patients

Condition

- Renal disorders (excl nephropathies)

Synonym
end stage renal disease, kidney transplant

Research involving
Human

Sponsors and support

Primary sponsor: Hansa Biopharma AB
Source(s) of monetary or material Support: Hansa Biopharma

Intervention

Keyword: Donor-specific antibodies, Imlifidase, Sensitised kidney transplant patients

Outcome measures

Primary outcome

1-year graft failure-free survival in patients who have been kidney

transplanted after imlifidase treatment

Secondary outcome

• Renal function at several time points between 24 hours and 2 weeks and at 1,

3 and 6 months and 1 year after transplantation as assessed by

estimated glomerular filtration rate (eGFR) and serum/plasma creatinine levels

• Patient survival at 1 year after transplantation

• Graft survival at 1 year after transplantation

• Proportion of patients with conversion of a positive crossmatch test to

negative within 24 hours after imlifidase treatment

• HLA/DSA antibody levels at several time points between pre-dose imlifidase

and 2 weeks, and at 1, 3 and 6 months and 1 year after imlifidase

treatment

• Imlifidase PK up to 14 days after imlifidase treatment

• Imlifidase PD up to 9 days after imlifidase treatment

• ADAs up to 1 year after imlifidase treatment

• Frequency of DGF

• Proportion of patients with biopsy- and serology (DSA)-confirmed AMRs over 1 year

• Proportion of patients with biopsy confirmed CMRs over 1 year.

• Safety over 1 year as measured by reported SAEs

• Safety assessed as proportion of patients with infusion-related reactions within 48 hours of imlifidase infusion

• Safety assessed as proportion of patients with severe or serious infections within 30 days after transplantation

• Change in patient-reported life participation, as measured by the PROMIS Social Health domain *Ability to participate in social roles & activities, PROMIS-SF-8a*, from baseline to 1 year after transplantation

Secondary endpoints relating to the non-comparative concurrent reference cohort

• Graft failure-free survival at 1 year after transplantation

• Renal function at 1, 3 and 6 months and 1 year after transplantation as assessed by eGFR and serum/plasma creatinine levels

• Patient survival at 1 year after transplantation

• Graft survival at 1 year after transplantation

• Frequency of DGF

• Proportion of patients with biopsy- and serology (DSA)-confirmed AMRs over 1 year

• Proportion of patients with biopsy confirmed CMRs over 1 year

• Safety over 1 year as measured by reported SAEs

• Safety assessed as proportion of patients with severe or serious infections within 30 days after transplantation

• Change in patient reported life participation, as measured by the PROMIS Social Health domain *Ability to participate in social roles & activities, PROMIS-SF-8a*, from baseline to 1 year after transplantation

Secondary endpoints relating to the randomly selected non-comparative historical reference cohort retrieved from the CTS registry

• Graft survival at 1 year after transplantation

• Renal function at 3 and 6 months, and 1 year as measured by serum/plasma creatinine category (<130 µmol/L, 130-259 µmol/L, 260-400 µmol/L and >400 µmol/L) (eGFR only available in selected patients)

• Patient survival at 1 year after transplantation

• Proportion of patients with rejection episodes (AMRs and CMRs) during the first post-transplant year in patients with a functioning graft at the end of the first posttransplant year

Study description

Background summary

This controlled, non-randomised, open-label post-authorisation trial is designed to provide comprehensive efficacy and safety data to support a full marketing authorisation of imlifidase (Idefirix®) in EU. The trial will include highly sensitised patients who will receive and accept crossmatch positive

kidney offers in line with the mode-of-action of imlifidase, i.e. conversion of a positive crossmatch to a negative crossmatch. The patients to be included are highly sensitised with the highest unmet medical need, unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients. The primary objective is to assess graft failure-free survival 1 year after transplantation in patients desensitised with imlifidase prior to kidney transplantation.

Kidney transplantation is considered the gold standard treatment of patients with chronic kidney disease (CKD). After kidney transplantation, patients live longer and experience a better quality of life (QoL) (Vo et al. 2013; Orandi et al. 2016). More than 30% of all patients waiting for a kidney transplant have developed antibodies of immunoglobulin G (IgG) type directed against foreign human leukocyte antigen (HLA) (Orandi et al. 2016). The main causes for this are previous organ transplantation, blood transfusion, infections, and pregnancy. Patients with a wide range of HLA antibodies with high titres, generating a calculated panel-reactive antibody (cPRA) value of >95%, are considered highly unlikely to be transplanted since the chance of finding an immunologically HLA-compatible donor is extremely low (EUROSTAM 2018).

Several therapeutic approaches have been tested to achieve desensitisation (Marfo et al. 2011), though many patients do not respond adequately to facilitate transplantation (Glotz et al. 2019; Sharma et al. 2016; Amrouche et al. 2017; Kute et al. 2011; Vo et al. 2008; Bartel et al. 2010; Marfo et al. 2012; Schwaiger et al. 2016). However, the treatments referred to, and other treatments in the literature, are experimental and are neither approved nor considered standard of care across the transplant community for the patient population to be included in the present trial, which is the patient population with the greatest unmet medical need. Currently, highly sensitised patients without a compatible living donor are placed on the waiting list and stay there for many years until they are delisted due to worsened comorbidity or death (Stewart et al. 2016; Schinstock et al. 2017).

The number of patients highly unlikely to receive a kidney transplant is estimated to be approximately 3000 in the EU (EUROSTAM 2018). These patients have an unmet medical need of a rapid, effective, and safe treatment to reduce the HLA antibodies, more specifically donor specific antibodies (DSA), to levels that would make them eligible for deceased donor kidney transplantation. Imlifidase was developed to meet this need and has been shown to remove DSA and convert positive crossmatch to negative in all highly sensitised patients treated so far (Jordan et al. 2017; Lorant et al. 2018; Lonze et al. 2018; Jordan et al. 2020).

Study objective

This study has been transitioned to CTIS with ID 2024-511810-18-00 check the CTIS register

for the current data.

Primary objective
• To determine the 1-year graft failure-free survival in highly sensitised kidney transplant patients, pre-treated with imlifidase to turn a positive crossmatch against a deceased donor negative

Secondary objectives relating to imlifidase treatment group
• To evaluate renal function up to 1 year after transplantation
• To evaluate patient survival 1 year after transplantation
• To evaluate graft survival 1 year after transplantation
• To evaluate crossmatch conversion within 24 hours of imlifidase treatment
• To evaluate HLA/DSA antibody levels up to 1 year after transplantation
• To evaluate pharmacokinetic (PK) profile of imlifidase
• To evaluate pharmacodynamic (PD) profile of imlifidase
• To evaluate immunogenicity profile of imlifidase (anti-drug antibodies [ADAs])
• To evaluate delayed graft function (DGF)
• To evaluate proportion of patients with biopsy- and serology-confirmed Antibody-Mediated Rejections (AMRs) up to 1 year after transplantation
• To evaluate proportion of patients with biopsy confirmed Cell-Mediated Rejections (CMRs) up to 1 year after transplantation
• To evaluate safety of imlifidase treatment with regards to reported serious adverse events (SAEs)
• To evaluate safety of imlifidase treatment with regards to infusion related reactions occurring within 48 hours of imlifidase infusion
• To evaluate safety of imlifidase treatment with regards to severe or serious infections occurring within 30 days after transplantation
• To evaluate health related quality of life (HRQoL) specifically patients* life participation

Secondary Objectives relating to the non-comparative concurrent reference cohort
• To evaluate graft failure-free survival 1 year after transplantation
• To evaluate renal function up to 1 year after transplantation
• To evaluate patient survival 1 year after transplantation
• To evaluate graft survival 1 year after transplantation
• To evaluate DGF
• To evaluate proportion of patients with biopsy- and serology-confirmed AMRs up to 1 year after transplantation
• To evaluate proportion of patients with biopsy confirmed CMRs up to 1 year after transplantation
• To evaluate number of reported SAEs up to 1 year after transplantation
• To evaluate proportion of patients with severe or serious infections within 30 days after transplantation
• To evaluate health related quality of life (HRQoL) specifically patients* life participation

Secondary Objectives relating to the randomly selected non-comparative

historical reference cohort retrieved from the CTS registry
• To evaluate graft survival 1 year after transplantation
• To evaluate renal function up to 1 year after transplantation
• To evaluate patient survival 1 year after transplantation
• To evaluate proportion of patients with rejection episodes during the first posttransplant year in patients with a functioning graft at the end of the first posttransplant year

Exploratory objective relating to the imlifidase treatment group and the concurrent reference cohort
• To evaluate HRQoL, specifically patients* anxiety, depression, fatigue, pain interference, physical function and sleep disturbance, self-reported ability to work, and general health status

Study design

This is an open label, non-randomised trial in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. 50 patients will be desensitised with imlifidase to convert a positive crossmatch to negative and then transplanted. The patients will receive 0.25 mg/kg imlifidase intravenously (IV) over a period of 15 minutes. One dose is adequate for most patients for crossmatch conversion, but if needed, a second dose may be administered within 24 hours. Following transplantation, patients will receive induction therapies (corticosteroids rabbit ATG), rejection prophylaxis (high-dose intravenous immunoglobulin (IVIg), rituximab or biosimilar) and maintenance immunosuppressive therapies. The patients will be followed for 12 months and evaluation of graft failure-free survival 1 year after transplantation is the primary objective. Other efficacy variables include renal function, patient survival, graft survival, crossmatch conversion, HLA/DSA levels, and health related quality-of-life. Safety variables include rejection episodes, adverse events of special interest (i.e., imlifidase infusion-related reactions and severe or serious infections), and serious adverse events (SAEs). Imlifidase pharmacokinetics, pharmacodynamics and immunogenicity will also be investigated.

Patients who, for any reason, are not transplanted after imlifidase treatment will not receive any post-transplantation therapy. All patients who receive imlifidase will remain in the trial and will be followed in accordance with the trial protocol even if they are not transplanted or if they lose their graft during the course of the trial. To compensate non-transplanted imlifidase patients, additional patients will be recruited in order to have 50 treated and transplanted patients.

Important clinical outcomes are 1-year graft failure-free survival and kidney function which reflect not the efficacy of imlifidase per se but effectiveness and safety in the real-world transplantation setting. However, it should be noted that this outcome is highly dependent on

the post-transplantation management of the patients, as well as compliance with respect to maintenance immunosuppressive regimen.

The rational for performing a non-randomised trial is that no other effective or approved desensitisation protocol exists in deceased-donor kidney transplantation that would provide a suitable control. In the absence of such treatment, randomisation between imlifidase and no imlifidase treatment (control) would randomise patients with a positive crossmatch to a nonconverting treatment, thus not allowing transplantation in these patients, and preventing comparison of transplant outcome.

Instead, a non-comparative reference cohort consisting of 50 to 100 concurrent kidney transplanted patients from participating trial sites with any grade of sensitisation and a negative crossmatch towards their donor will be enrolled in the trial. The rationale for including the non-comparative, prospective, reference group is to address differences in-site practice and experience that may have an impact on the overall results for the imlifidasetreated cohort. Also, the difference in the extent of immunosuppressive therapies given in the two cohorts will be addressed. Once a highly sensitised imlifidase treated patient has been transplanted subsequent patients who are offered a compatible kidney will also be offered the opportunity to be included in the trial as part of the reference group and transplanted. The goal is to have at least 1 or 2 patients per imlifidase treated patient from each site participate in the concurrent control group. Given that the patients in this reference cohort will be qualitatively different from the imlifidase treated patients, formal statistical comparisons will not be appropriate. Hence, data from these patients will be collected for descriptive purposes only. Following completion of the trial, and where possible, patients will be matched in terms of relevant, baseline prognostic factors that can have an influence on graft and patient survival. The concurrent control patients will be followed for 12 months after transplantation
(5 clinic visits) and treated in accordance with each clinic*s normal transplantation routines. Efficacy variables followed in this cohort include graft failure-free survival, patient survival, graft survival, renal function and health related quality of life. The safety variables include rejection episodes, adverse events of special interest (i.e., severe or serious infections), and SAEs.

A second, non-comparative historical reference cohort of 100 kidney transplanted patients will be randomly selected from the Collaborative Transplant Study (CTS) registry. These patients will be less sensitised (cut off PRA >=50%) compared to the current imlifidase cohort, have a negative crossmatch towards their donor and by that have been transplanted. However, outcome variables investigated in this cohort including 1-year graft survival, renal function, patient survival and assessments of rejection episodes during the first year will address the outcome in a sensitized cohort even though less sensitised than in the imlifidase treatment group. Since patients in this

cohort are expected to have both a better prognosis and a higher graft survival rate at 1 year than the imlifidase-treated patients, formal statistical comparison between the groups would be inappropriate.

The ELITE-Symphony trial investigated the 1-year eGFR with different maintenance immunosuppression treatments (Ekberg et al. 2007). This publication had a major impact on the transplant community and moved the general immunosuppression towards primary use of low dose tacrolimus together with prednisolone and mycophenolate mofetil (MMF). The year 2010 was chosen as cut-off for inclusion in the historical reference cohort to make it likely that the patients in this group have received the same maintenance immunosuppression as is given today to most kidney transplant recipients.

Intervention

Imlifidase will be administered as a single IV infusion, 0.25 mg/kg, over a period of 15 minutes. A second dose may be administered within 24 hours of the first dose if the first dose is considered to have insufficient effect. The transplant needs to occur within 24h after imlifidase treatment.

Study burden and risks

Patients in this trial are highly sensitised with the highest unmet medical need, unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients. These patients may benefit from being treated with imlifidase to remove HLA antibodies and enable kidney transplantation. The potential benefit of imlifidase over currently used methods for desensitisation includes the extremely efficient inactivation of HLA antibodies including DSAs also for patients who are highly sensitised with high antibody concentrations. This will enable transplantation in a patient group with virtually no other options. To date, a total of 46 patients in clinical studies have been transplanted after treatment with imlifidase. Imlifidase was well-tolerated, with only few related adverse events (AEs) reported and no clinically significant safety findings.

Taking into account the measures taken to minimise risk to patients participating in this clinical trial, the potential risks identified in association with imlifidase treatment are justified by the anticipated benefits that may be offered to highly sensitised patients waiting for a kidney transplant.

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 all patients
1. Male or female patient aged 18-75 years
2. ABO-compatible deceased donor aged 10-70 years
3. Signed Informed Consent obtained before any trial related procedures
4. Willingness and ability to comply with the protocol
Inclusion Criteria for imlifidase patients
1. End-stage renal disease (ESRD) active on the renal transplant waiting list of a kidney
allocation system at the time of screening
2. High sensitisation with the highest unmet medical need unlikely to be transplanted
under the available kidney allocation system including prioritisation programmes for
highly sensitised patients (see table below for recommended reference thresholds. Note: highest unmet medical need is per investigator's discretion)

3. Known DSA against an available deceased donor
4. Positive crossmatch test determined by Complement-Dependent Cytotoxicity crossmatch (CDCXM) and/or Flow Cytometry Crossmatch (FCXM) against an available deceased donor. If physical crossmatch tests are not practically possible due
to lack of time, patients may be included on a Virtual Crossmatch (vXM) predictive
of a positive crossmatch test.
Inclusion Criteria for patients in the non-comparative concurrent reference cohort
1. Active on the renal transplant waiting list at a participating trial site at the time of
screening
2. An acceptable kidney transplant from a deceased donor

Exclusion criteria

Exclusion Criteria for imlifidase patients
1. Previous treatment with imlifidase
2. Previous high dose IVIg treatment (2 g/kg) within 28 days prior to imlifidase treatment
3. Suspicion of Covid-19 infection or positive SARS-CoV-2 test
4. Breast feeding or pregnancy
5. Hypersensitivity to the active substance (imlifidase) or to any of the excipients
6. Ongoing serious infections (including HBV, HCV, CMV, EBV, tuberculosis)
7. Present, or history of, thrombotic thrombocytopenic purpura (TTP), or known familial history of TTP
8. Severe other condition requiring treatment and close monitoring e.g. cardiac failure
>= grade 4 (New York Heart Association), unstable coronary disease or oxygen dependent respiratory disease
9. Female of childbearing potential, not willing to use effective contraception during the
3 weeks following treatment with imlifidase. In the context of this trial, an effective
method is defined as those which result in low failure rate (i.e. less than 1% per year)
when used consistently and correctly.
10. Any other reason that, in the view of the investigator, precludes transplantation

Exclusion Criteria for imlifidase patients and for patients in the non-comparative
concurrent reference cohort

1. Use of investigational agents within 5 terminal elimination half-lives prior to the
transplantation
2. Malignancy within 5 years prior to transplantation
3. Positive serology for human immunodeficiency virus (HIV)
4. Clinically relevant active infection(s) (including hepatitis B [HBV], hepatitis C [HCV], cytomegalovirus [CMV], Epstein Barr Virus [EBV], tuberculosis) as judged by the investigator
5. Contemporaneous participation in medical device studies
6. Known mental incapacity or language barriers precluding adequate understanding of
the Informed Consent information and the trial activities
7. Inability by the judgement of the investigator to participate in the trial for any other
reason

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-10-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Idefirix

Generic name:	Imlifidase
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-06-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-09-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-01-2024
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
EU-CTR	CTIS2024-511810-18-00
EudraCT	EUCTR2021-002640-70-NL
CCMO	NL79830.078.22