Medicinrådet

Bilag til Medicinrådets anbefaling vedr. imlifidase til nyretransplantation

Desensibiliseringsbehandling af yderst sensibiliserede voksne nyretransplan-tationspatienter med positiv krydsmatch overfor en tilgængelig afdød donor

Vers. 1.0

Bilagsoversigt

1. Ansøgers endelige ansøgning vedr. imlifidase til nyretransplantation

Application for the assessment of imlifidase (Idefirix®) for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor

All text and material referred to as "data on file" and marked with yellow are strictly confidential and should be deleted before publication.

HANSA BIOPHARMA

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Idefirix®
Generic name	Imlifidase
Marketing authorization holder in Denmark	Hansa Biopharma AB
ATC code	L04AA41
Pharmacotherapeutic group	Immunosuppressants
Active substance(s)	Imlifidase
Pharmaceutical form(s)	Powder for concentrate for solution for infusion (1)
Mechanism of action	Imlifidase is a cysteine protease derived from the immunoglobulin G (IgG)-degrading enzyme of Streptococcus pyogenes that cleaves the heavy chains of all human IgG subclasses but no other immunoglobulins. The cleavage of IgG leads to elimination of Fc-dependent effector functions, including complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). By cleaving all IgG, imlifidase reduces the level of DSA's, thus enabling transplantation (1).

Overview of the pharmaceutical	
Dosage regimen	The dose is based on patient body weight (kg). The recommended dose is 0.25 mg/kg administered as a single dose preferably within 24 hours before transplantation. One dose is adequate for crossmatch conversion in most patients, but if needed, a second dose can be administered within 24 hours after the first dose (1).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Imlifidase is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Imlifidase should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients (1).
Other approved therapeutic indications	Imlifidase is not approved for other indications.
Will dispensing be restricted to hospitals?	Yes, imlifidase is restricted to hospital use only.
Combination therapy and/or co-medication	Premedication with corticosteroids and antihistamines should be given to reduce the risk of infusion reactions in accordance with transplant centre routines. Since respiratory tract infections are the most common infections in patients with hypogammaglobulinemia, prophylactic oral antibiotics covering respiratory tract pathogens should be added to the standard of care for four weeks. Patients treated with imlifidase should, in addition, receive standard of care induction T-cell depleting agents with or without B-cell depleting agents.
Packaging – types, sizes/number of units, and concentrations	Imlifidase is supplied as a glass vial containing a powder for concentrate for solution for infusion (powder for concentrate). The powder is a white freeze-dried cake. Each vial contains 11 mg of imlifidase. After reconstitution, each mL of concentrate contains 10 mg imlifidase. Packs contain 1 or 2 vials.
Orphan drug designation	Imlifidase was designated an orphan medicine on 12 January 2017.

2. Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AIC	Akaike information criterion
AMR	Antibody medicated rejection
APD	Automated peritoneal dialysis
ATG	Anti-thymocyte globulin
ATTOM	The Access to Transplantation and Transplant Outcome Measures
AUC	Area under the plasma concentration versus time curve
BIA	Budget impact analysis
BIC	Bayesian information criterion
CAPD	Continuous ambulatory peritoneal dialysis
CDC	Complement-dependent cytotoxicity

CI	Confidence interval
CKD	Chronic kidney disease
CL	Clearance
Cmax	Maximum observed plasma concentration
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
cPRA	Calculated panel-reactive antibodies
CSR	Clinical study report
CU	Cost-utility
CUA	Cost-utility analysis
CVC	Central venous catheter
CXM	Crossmatch
DD	Deceased Donor
DEXA	Dual-energy x-ray absorptiometry
DMC	Danish Medicines Council
DRG	Diagnose-related group
DSA	Donor-Specific Antibodies
EBV	Epstein-Barr virus
ECD	Extended Criteria Donors
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
EPAR	European public assessment report
ESRD	End-stage renal disease
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
FDA	Food and drug administration
GFR	Glomerular filtration rate
HD	Haemodialysis dialysis
HR	Hazard ratio
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
HUT	Highly sensitised, unlikely to be transplanted
ICER	Incremental cost-effectiveness ratio
IEC	Ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicinal product
IQR	Interquartile range
IRB	Institutional Review Board
ITC	Indirect treatment comparison
IV	Intravenous
IVIg	Intravenous immunoglobulin G
KDQOL-SF	Kidney Disease Quality of Life-Short Form

LAMP	Local Acceptable Mismatch Program
LD	Living Donor
LY	Life years
MDRD	Modification of diet in renal disease
MESH	Medical subheadings
MFI	Mean fluorescent intensity
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
NHS	National Health Service
NICE	The National Institute for Health and Clinical Excellence
NYHA	New York Heart Association
OWSA	One-way sensitivity analysis
PD	Peritoneal Dialysis
PK	Pharmacokinetic
Plasmapheresis	PLEX
PP	Per-protocol
PPP	Pharmacy purchase price
PRA	Panel-reactive antibodies
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled study
RR	Relative risk
RRT	Replacement therapy
RTX	Rituximab
SAB	Single antigen bead
SAE	Serious adverse event
sclgG	Single-cleaved IgG
SD	Standard deviation
SE	Standard error
SoC	Standard of care
SPC	Summary of product characteristics
SPK	Simultaneous (combined) pancreas and kidney
SS	Sum of squares
STAMP	Scandiatransplant Acceptable Mismatch Program
Tac	Tacromilus
TB	Tuberculosis
t-CDC	Complement-dependent lymphocytotoxic
TEAE	Treatment Emergent Adverse Event
Tmax	Time point for maximum observed plasma concentration
UKRR	UK Renal Registry
UNOS	United Network for Organ Sharing
UT	Unlikely to be Transplanted
VSS	Volume of distribution at steady state
Vz	Volume of distribution during the elimination phase
XM	Crossmatch

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4. Summary

Chronic kidney disease (CKD) is a disease where patients gradually lose kidney function. End-stage renal disease (ESRD) is the term when chronic kidney failure progresses to a kidney function with glomerular filtration rate (eGFR) <15% of capacity and dialysis or a kidney transplantation is required to sustain life. ESRD is the most severe stage of CKD. The treatment options for patients with ESRD are dialysis or kidney transplantation. Kidney transplantation is the preferred treatment option for ESRD patients, as it increases survival and quality of life (QoL). However, some ESRD patients have an immunologic barrier to transplantation because they have antibodies against human leukocyte antigen (HLA). The introduction of imlifidase opens up the possibility of kidney transplantation to patients who would otherwise not be eligible for transplantation.

Imlifidase is a cysteine protease that cleaves the heavy chains of all human IgG subclasses but no other immunoglobulins. Imlifidase is indicated for desensitisation of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. Treatment with imlifidase reduces the level of anti-HLA antibodies, including donor-specific antibodies (DSAs) (HLA antibodies directed against HLA antigens of the donor), thus enabling transplantation in highly sensitised patients with positive crossmatch (1). The use of imlifidase should be reserved for patients unlikely to be transplanted under the available kidney allocation system, including prioritisation programmes for highly sensitised patients (1). Antibodies against the donor's graft are a major obstacle to successful transplantation in patients with kidney failure. Patients who are highly sensitised therefore usually remain on dialysis with shorter life expectancy and poor quality of life. In light of this and despite the need for further data, the European Medicines Agency (EMA) granted imlifidase a conditional marketing authorisation in 2020. This was granted in the interest of public health, because imlifidase addresses an unmet medical need and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required (the conditional approval was granted already after phase 2 studies based on the large unmet need, and it was not appropriate to wait for phase 3 to be completed) (2).

The patient population in this assessment are Danish adult patients (≥18 years) with CKD, awaiting a kidney transplant from a deceased donor, who are highly sensitised (panel-reactive antibodies (PRA) ≥80%), eligible for inclusion in STAMP/LAMP and have anti-HLA antibodies, making them unlikely to receive a compatible donor organ even through STAMP and/or LAMP due to a positive crossmatch with the donor. Currently, there is no alternative treatment options for removal of anti-HLA antibodies in deceased donor transplantation. Instead, patients receive best supportive care, which in Denmark consists of dialysis. In the current health economic model, we compared imlifidase to dialysis. However, no comparative analyses of efficacy and safety for imlifidase and best supportive care were presented in the application.

To assess the efficacy and safety of imlifidase, we applied results from the long-term Study 14 and results from a pooled analysis including the four phase II studies: Study 02, Study 03, Study 04 and Study 06. Study 14 was used to assess the efficacy of imlifidase in terms of graft survival, patient survival and quality of life (QoL), and the pooled analysis was used to assess the efficacy of imlifidase in terms of DSA elimination, crossmatch conversion and kidney function (measured with eGFR). Safety results on antibody-mediated rejection (AMR), adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs) and discontinuation were presented for each individual study. In the health economic model, we applied survival data on imlifidase from Study 14 and survival data on dialysis from Chaudhry et al. 2022 in the base case (3). Phase 3 data was not available at the time of preparing the DMC application, nor the five-year follow-up, and Hansa Biopharma does recognise that the data package is not complete. EMA still granted conditional approval with limited data (and without the three-year data) due to the level of unmet need, and it was not appropriate to wait. The three-year data is the longest-term clinical trial data in the area of highly sensitised kidney transplantation, which represents an ultra-rare indication, and as such, it is common practice to be able to

make decisions based on data from a limited number of patients. What makes this situation different with considerable uncertainty are two aspects: 1) the intervention (imlifidase) is estimated to have an ICER of DKK 43,597 per QALY in the base case. Thus, the distance up to an acceptable ICER is considerable and can contain large amounts of uncertainty before the ICER reaches levels where decision-making starts to become difficult. 2) imlifidase demonstrates 100% efficacy in enabling transplantation in a very difficult to transplant population (including patients with 100% cPRA). Taking this into consideration, those two aspects reduce the uncertainty in this case, and putting the uncertainty into perspective is an important part of a fair HTA assessment.

The health economic analysis conducted in the present application was a cost-utility (CU) analysis estimating the cost per incremental QALY for patients treated with imlifidase and receiving subsequent kidney transplantation as compared to patients remaining on best supportive care receiving dialysis therapy. The model consisted of three health states: 1) dialysis (haemodialysis, home haemodialysis, or peritoneal dialysis), 2) functioning graft and 3) death. The patient cohort entered the model in one of two ways: 1) as patients that were not treated with imlifidase and enter the model on dialysis. The majority of patients who enter the model on dialysis will not receive a kidney transplant; however, to reflect Danish clinical practice, a small percentage of patients in the dialysis arm received a transplantation within the first two years in the model and the remaining continued receiving dialysis until death, or 2) as patients treated with imlifidase and with a post-imlifidase negative crossmatched kidney transplant. Patients who underwent transplantation remained in the 'functioning graft' health state until they lost their graft and transitioned to dialysis therapy. Patients who lost their graft could not regain it and remained on dialysis until death.

The patient survival of highly sensitised patients who are transplanted compared to those who stay on dialysis has been discussed with the DMC in the validation phase. The DMC has argued that survival is expected to be similar between highly sensitised transplanted patients if compared to a similar patient population who remain in dialysis treatment with a reference to the study by Manook et al. 2017 (4). Manook et al. 2017 compared survival of patients opting for an HLA-incompatible (HLAi) kidney transplant with that of similarly sensitised patients awaiting a compatible organ (while being on dialysis). Manook et al. 2017 reported no difference in the survival of sensitised patients undergoing HLAi transplantation compared with those on dialysis awaiting a compatible organ, many of whom are unlikely to be transplanted.

It should be noted that only a very small number of patients were observed beyond four years, and Manook et al. 2017 can therefore not be used as a reliable long-term study. In addition, there is a large amount of literature stating the opposite, i.e., that a similar patient population on dialysis does not have a survival similar to highly sensitised transplanted patients. The dialysis mortality is worse than transplantation, even in the population of dialysis patients who are fit for transplant and on the transplant waiting list. Figure 1 presents Kaplan-Meier estimates of patient survival from the 2020 annual report form the Norwegian Renal Registry (5). The Norwegian Renal Registry is an epidemiology quality register for Norwegian patients with severe renal disease and follows patients for their entire life course. As seen in Figure 1, the patient survival for patients receiving a transplantation is much higher compared to patients who remain on dialysis – a survival benefit that is present in both the population with patients on dialysis who are candidates for a transplantation and who are not candidates for a transplantation. In addition, the 2018 ERA-EDTA Registry Annual Report (6) presents an adjusted five-year patient survival for deceased donor transplantation of 92.0% (95% CI 91.7–92.3), while an unadjusted five-year patient survival for dialysis is 42.6% (95% CI 42.5–42.7). The real-world data from the Norwegian Renal Registry and the ERA-EDTA Registry demonstrates that there is a survival difference in patients being transplanted and patients receiving dialysis in favour of transplantation.

In the model base case, data from all 46 patients who underwent a kidney transplant studied within the imlifidase clinical trials was used to estimate the survival with a functioning graft, while the DMC's standpoint of a similar patient

survival for transplantation and dialysis was accommodated by including a scenario analysis in which the patient survival with a functioning graft and dialysis was estimated based on transplantation mortality rates from Boenink 2020 (7).

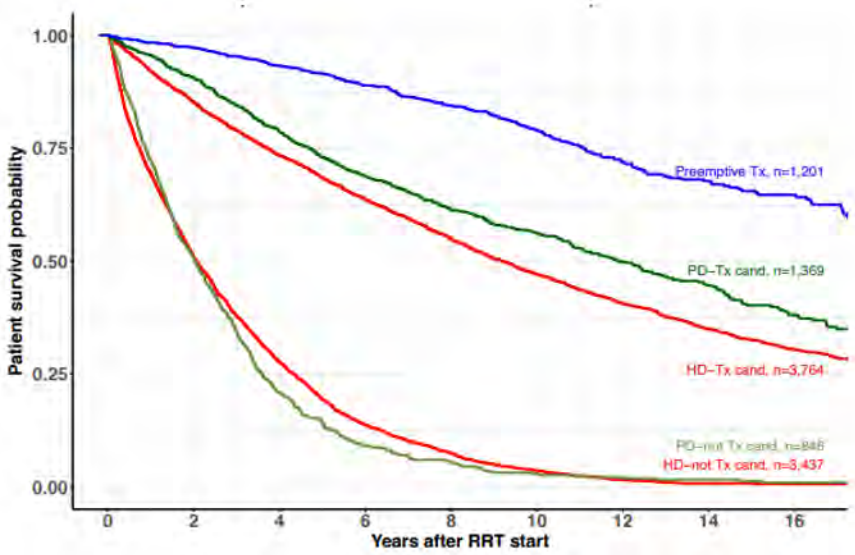

Figure 1: Patient survival in renal replacement therapy (RRT) by transplantation assessment and 1st treatment, Norway 2000–2020. Source: Annual report from the Norwegian Renal Registry 2020 (5).

Treatment with imlifidase and subsequent transplantation was associated with a markedly increase in QALY of 3.57 and a small incremental cost (DKK 155,849), making treatment with imlifidase a cost-effective treatment choice. Uncertainty in the input parameters in the health economic model was explored through extensive sensitivity analyses. In the one-way sensitivity analyses (OWSA), we found that some parameters could influence the results by a rather large margin; however, these margins were well balanced across the base case estimate. The parameters that were the most influential were the cost of dialysis per cycle, the HR of death for patients on dialysis as compared to patients receiving transplantation and proportion of haemodialysis patients. In addition, several different scenarios were explored to investigate the result using alternative model specifications. Moreover, the PSA showed that imlifidase remained cost-effective in most iterations when testing the impact of the combined uncertainty of all model input parameters.

The budget impact of recommending imlifidase as standard treatment for highly sensitised patients who are unlikely to receive a kidney was DKK 26,369,446 in the first year, DKK 15,603,246 in year 2, DKK 13,965,686 in year 3, DKK 12,484,422 in year 4, and DKK 11,162,294 in year 5.

5. The patient population, the intervention and choice of comparator(s)

CKD is a disease where patients gradually lose kidney function. ESRD is the term when chronic kidney failure progresses to a kidney function with eGFR <15% of capacity and dialysis or kidney transplantation is required to sustain life. ESRD is the most severe stage of CKD. The clinical presentation of ESRD involves alterations in the fluid, electrolyte and acid-base balances and accumulation of nitrogenous compounds such as serum urea and serum creatinine. ESRD can manifest as symptoms in almost all organ systems, with the most common symptoms being fatigue, nausea and reduced appetite, followed by weight loss (8,9). ESRD is associated with a risk of severe complications such as cardiovascular disease and death (10).

The treatment options for patients with ESRD are dialysis or kidney transplantation. To ensure the right match before transplantation, a crossmatch test is performed where target cells from the donor (typically from peripheral blood, lymph node or spleen) are mixed with serum from the intended recipient to test the risk for acute rejection due to high levels of donor-specific antibodies (DSAs) (human leukocyte antigen (HLA) antibodies directed against HLA antigens of the donor) (11). The major histocompatibility complex (MHC) encodes two main classes of cell surface antigens: HLA class I and II, whose function is to present peptides to T cells and antigen-presenting cells, allowing tolerance for self-antigen-expressing cells and elimination of non-self-antigens. Class I HLA is expressed on all nucleated cells and platelets and includes HLA-A, HLA-B and HLA-C. Class II HLA is expressed on specialised antigen-presenting cells such as B cells, macrophages and dendritic cells and includes HLA-DR, HLA-DQ and HLA-DP (12). Kidney transplantation with pre-formed DSA can lead to hyperacute AMR starting immediately after reperfusion of the transplant, resulting in graft failure and return to dialysis. Therefore, all ESRD patients on the kidney transplant waiting list are evaluated to determine their degree of sensitisation. This is done by analysing the number of panel-reactive antibodies (PRA) or calculated PRA (cPRA). Some ESRD patients have an immunologic barrier to transplantation because they have antibodies against HLA. These patients are categorised as sensitised. Four levels of sensitisation may be used: non-sensitised, sensitised, highly sensitised and low or previously sensitised (13,14). In Denmark, highly sensitised patients are defined based on PRA ≥80% (statement from Danish clinical expert and Scandiatransplant). Highly sensitised patients are eligible for inclusion in the Scandiatransplant Acceptable Mismatch Program (STAMP), or the local programme LAMP, based on a transplantability score. The eligibility criteria for inclusion in STAMP/LAMP is a transplantability score ≤2% and ABO compatible ≤3% (15). The transplantability score is based on split-level HLA typing on the patient and defined acceptable mismatches. The score provides the percentage of donors who are ABO-identical or compatible and have HLA split-level antigens that are acceptable to the recipient (recipient HLA + acceptable mismatches) (15).

In 2020, data from STAMP (which includes Danish patients) showed that the waiting time for kidney transplantation for highly sensitised patients (PRA ≥80%) were on average 2.4 times longer than for non-sensitised patients (40 vs 17 months), while sensitised patients (PRA ≥10% and <80%) on average waited 1.3 times longer than non-sensitised patients (22 vs 17 months) (16). Normally, patients receive dialysis while on the waiting list. The time on dialysis substantially impacts patients' quality of life (QoL), graft success, and survival. Moreover, dialysis is associated with many complications and side-effects such as anaemia, amyloidosis and infections, which get worse with time on dialysis (17–26). Death rates for patients at high immunologic risk remaining on dialysis are consistently higher than patients who undergo desensitisation and transplant (27). Similarly, survival rates are lower for patients on dialysis than for kidney transplant recipients. In the long term, patients may become ineligible for dialysis due to failed ports or veins or other factors, creating an urgent and immediate need for transplantation (25). Patients who discontinue dialysis die within 1–2 weeks (28). In Denmark, the mortality of chronic dialysis patients is approximately 20% per year (29). The population of highly sensitised patients with a transplantability score ≤2% currently has no alternative options for desensitisation, since there is no efficient authorised treatment for removing the anti-HLA antibodies, and is therefore unlikely to be transplanted, resulting in a life on dialysis.

The incidence of CKD in Denmark has been stable since 2000, with approximately 700 new cases per year, while the prevalence of CKD has increased yearly, likely due to the improved treatment of diabetes and cardiovascular disease and increased average lifetime. In Denmark, approximately 5000 patients (0.1% of the Danish population) receive treatment related to ESRD (30), and approximately 500 patients are on the waiting list for a new kidney (9). In recent years, the incidence of ESRD in Denmark has stabilised (30).

The Danish patient population relevant for imlifidase is highly sensitised adult patients (≥18 years) awaiting kidney transplantation who, due to their broad anti-HLA antibody profile, are unlikely to receive a compatible donor organ through the local or Scandiatransplant allocation programmes, including STAMP and/or LAMP. No established definition of unlikely to be transplanted through STAMP and LAMP exists, which makes it difficult to estimate the number of Danish patients who are candidates for imlifidase treatment. Koefoed-Nielsen et al. 2017 (31) assessed data from patients included in the STAMP/LAMP from 2009 and 2015. From 2009 to 2015, 248 patients were given STAMP priority (according to the criteria at that time). At the end of the period, approximately half of these patients were transplanted: 133 patients (53.6%) were transplanted with a kidney from a deceased donor, and 96 of these transplantations were through STAMP and 37 through LAMP. At the end of the six-year period, 94 patients (37.9%) were still on the waiting list, nine patients (3.6%) were permanently withdrawn from the waiting list and 11 patients (4.4%) died while waiting for a kidney transplant (31). Of the 96 transplantations through STAMP in the study period, 29 patients with a transplantability score ≤0.2% were transplanted with an average waiting time of 205 days (6-583 days). However, even though patients with a transplantability score ≤0.2% were transplanted in the study, this particular subgroup of highly sensitised patients is accumulating on the STAMP waiting list, and the waiting time increases as the transplantability score decreases (31).

According to Scandiatransplant numbers from Q1 of 2022, around 514 Danish patients are on the waiting list to receive a new kidney (32). Based on a dialogue with the Danish Medicines Council (DMC), we believe that approximately 10% of these patients are highly sensitised, corresponding to 51 patients. We consulted a clinical expert on the number of patients in Denmark who are highly sensitised and currently unlikely to be transplanted under STAMP/LAMP, and therefore potential candidates for imlifidase. The clinical expert informed that approximately 2 (corresponding to [redacted] Danish patients) are unlikely to receive a kidney under STAMP/LAMP. Given the scarcity of organs and the complexity of incompatible transplantations, only a small handful of this total pool of patients can be transplanted each year. There will also be a small inflow of new highly sensitised patients to the waiting list each year (approximatly 2-3 patients), but there is also an outflow driven by both mortality and patients taken off the waiting list due to patients no longer being fit for transplantation. Due to the limited size of the population, the assumption is that the prevalence has been somewhat constant during the last five years, and that observed trends will persist over the coming years. However, according to the clinical expert, the number of highly sensitised patients waiting for a kidney has accumulated over the last few years, resulting in the currently higher prevalence. These patients have no living donor, and inactivation of immunoglobulin G (IgG) with imlifidase enables deceased donor transplantation with an HLA-incompatible organ. These patients, who are unlikely to be transplanted through the STAMP (or LAMP) programme due to a very low transplantability score, could benefit from imlifidase.

In Table 1 and Table 2 we have listed the incidence and prevalence of patients relevant for imlifidase from the last five years and an estimate of the number of eligible patients in the next five years, respectively.

Table 1: Incidence and prevalence in the past five years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	[redacted]	5	[redacted]	[redacted]	[redacted]
Prevalence in Denmark	5	5	[redacted]	[redacted]	[redacted]

Table 2: Estimated number of patients eligible for imlifidase in the next five years

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to use Idefirix® in the coming years	1	8	●	●	6

Note: The numbers in Table 1 and Table 2 are based on input from a clinical expert. The clinical expert informed that the number of highly sensitised patients waiting for a kidney has accumulated over the last few years, resulting in a higher prevalence in 2022.

5.1.1 Patient populations relevant for this application

The relevant patient population for this application is Danish adult patients (≥18 years) with CKD, awaiting a kidney transplant from a deceased donor, who are highly sensitised (PRA ≥80%), eligible for inclusion on STAMP/LAMP, and have anti HLA antibodies, which makes them unlikely to receive a compatible donor organ even through STAMP and/or LAMP due to a positive crossmatch with the donor.

According to a clinical expert, around 10 Danish patients are currently eligible for imlifidase. The Danish patient population eligible for imlifidase has a mean age of 45 years, and 60% will be female as female patients tend to become sensitised due to pregnancies. Moreover, the clinical expert estimated that around 20% of the eligible patients will weigh more than 88 kg.

A subgroup of patients who are unlikely to be transplanted (HUT) has been examined in a post-hoc analysis. The analysis defined the "HUT-subgroup" as patients with cPRA ≥95% and positive crossmatch against a deceased donor organ and consisted of 25 patients. This subgroup has been included in a scenario analysis in the health economic analysis.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The current treatment options for patients with ESRD are dialysis or kidney transplantation. Dialysis cleans the blood of waste products, which the kidneys do in healthy individuals. Two types of dialysis exist; haemodialysis (HD) and peritoneal dialysis (PD), and in Denmark, HD is the most frequently used type (approximately 80% of chronic kidney patients in dialysis) (29,33). HD is typically done at a dialysis department at the hospital, where the blood is pumped through a machine (dialyser) to filter waste products from the blood (but a small number of patients receive HD at home) (29). Patients typically receive HD three to four times per week (29). PD involves a plastic tube placed in the abdominal cavity which is used to inject a cleansing fluid into the abdomen. The peritoneum acts as the membrane for exchanging fluid and dissolved substances with the blood. After a set period of time, the fluid with the filtered waste products is flushed out of the abdomen and is discarded. PD is performed daily and used by approximately 20% of chronic kidney patients in Denmark (29,33). PD is typically managed by patients or caregivers at home (29). When PD is no longer sufficient, and prior to the patient switching permanently to HD, patients can receive hybrid dialysis consisting of daily PD in combination with HD 1-2 times weekly. Switches between the types of dialysis can happen both ways. Switches from PD to HD typically happens due to complicated infections (e.g., peritonitis), abdominal

operations or insufficient dialysis quality (29). Switches from HD to PD is typically due to lack of sufficient vascular access or patients' preference for more self-determination in their treatment (29). Both HD and PD are associated with complications and side effects such as cardiovascular disease, anaemia, amyloidosis and infections, which get worse with time on dialysis (26,34). Long-term dialysis can lead to patients eventually losing access to dialysis due to failed ports or veins and other factors which results in an urgent and immediate need for transplantation (25).

Kidney transplantation is the preferred treatment option for ESRD patients, as it increases survival and QoL while resulting in substantial savings in healthcare costs compared to dialysis (17,18,35). All Danish patients suitable for kidney transplantation are enrolled on the Scandiatransplant waiting list. When a kidney becomes available, a prioritised order of recipients with the best match is formed (9). The transplanted kidney can come from either a living or a deceased donor, but most kidney transplants are done with a deceased donor (35% and 65% of kidneys are from living and deceased donors, respectively) (9). All patients receive immunosuppressive treatment prior to the transplantation. In Denmark, this consists of an induction treatment with basiliximab or anti-thymoglobuline followed by a multiple drug treatment (typically a combination of tacrolimus and mycophenolate mofetil and potentially steroid based on local tradition) (36). A crossmatch test is performed prior to the kidney transplantation where target cells from the donor (normally from peripheral blood, lymph node or spleen) are mixed with serum from the intended recipient to test the risk for acute rejection due to high levels of DSAs (HLA antibodies directed against HLA antigens of the donor) (11). Patients' ability to receive kidney transplantation is a multifactorial judgment. The probability of undergoing transplantation is affected by several factors, including the patient's HLA makeup, HLA antibody profile and grade of sensitisation, blood group, geographic location and estimated remaining time on the waiting list. Sensitisation to HLA is a major barrier to kidney transplants, because finding a deceased donor match is difficult. Currently, there are no alternative options for desensitisation, as no efficient authorised treatment for the removal of the anti-HLA antibodies currently exists.

5.2.2 Choice of comparator(s)

Currently, there is no alternative treatment option for a fast removal of anti-HLA antibodies as is necessary in the deceased donor setting; thus, highly sensitised patients are unlikely to receive a deceased donor kidney transplant. Instead, patients will receive best supportive care, which in Denmark consist of HD and PD dialysis. Dialysis is the established best supportive care for the specified patient population without imlifidase.

As there are currently no appropriate comparators available for desensitisation treatment for highly sensitised patients with ESRD awaiting kidney transplantation from a deceased donor in Denmark, the choice of comparator has been discussed with the DMC at the dialogue meeting. In the health economic model, the comparison will be conducted with the current best supportive care for these patients; HD and PD dialysis. However, no comparative analyses of efficacy and safety will be presented in the application.

5.2.3 Description of the comparator(s)

HD is typically done at a dialysis department at the hospital, where the blood is pumped through a machine (dialyser) to filter waste products from the blood (29). HD patients' blood is brought into contact with the dialysis fluid. Blood and dialysis fluid are only separated by a semipermeable membrane. Metabolism between blood and dialysis fluid takes place by either diffusion (haemodialysis) or filtration (hemofiltration) through the membrane. The two techniques are often combined. Patients normally receive HD three to four times per week. HD is a lifelong treatment, unless patients switch to PD or receive a kidney transplant (29).

PD is typically managed at home. Patients have a plastic tube placed in the abdominal cavity which is used for the in- and out-flow of dialysis fluid. The peritoneum acts as the membrane for exchanging fluid and dissolved substances with the blood. After a set period of time, the fluid with the filtered waste products is flushed out of the abdomen and discarded, and patients can flow in new cleansing fluid. Patients normally receive PD three to four times a day, and each exchange takes around half an hour. PD is a lifelong treatment, unless patients switch to HD or receive a kidney transplant (29). An overview of the two types of dialysis is provided in Table 3.

Table 3: Description of HD and PD dialysis

	HD dialysis	PD dialysis
ATC-code	B05Z	B05D
Mode of action	Metabolism between blood and dialysis fluid takes place by either diffusion (haemodialysis) or filtration (hemofiltration) through the membrane. The two techniques are often combined.	The peritoneum acts as the membrane for exchanging fluid and dissolved substances with the blood. The fluid with the filtered waste products is flushed out of the abdomen and discarded.
Pharmaceutical form	Fluid	Fluid
Method of administration	At a dialysis department at the hospital. The blood is pumped through a dialyser to filter waste products from the blood. HD access is through the arm.	PD is typically managed at home. PD involves a plastic tube being placed in the abdominal cavity which is used to flow in a cleansing fluid into part of the abdomen and flow out the fluid and filtered waste products.
Dosing	Three to four times per week for three to four hours.	Daily, three to four times each day. Each exchange takes about 30 minutes.
Should the pharmaceutical be administered with other medicines?	On dialysis, patients additionally continue the CKD treatment as administered prior to dialysis.	On dialysis, patients additionally continue the CKD treatment as administered prior to dialysis.
Treatment duration/criteria for end of treatment	Lifelong treatment or until transplantation or switch to PD dialysis	Lifelong treatment or until transplantation or switch to HD dialysis
Necessary monitoring, both during administration and during the treatment period		Patients will be trained in the managing of the PD dialysis at the hospital before being sent home. In the beginning of PD, dialysis patients will have ambulant control visits once a week. Later, the controls will be every four to eight weeks.

Need for diagnostics or other tests (i.e., companion diagnostics)	None	None
Packaging	The dialysis solution is packed in a bag.	The dialysis solution is packed in a bag.

5.3 The intervention: Imlifidase

Introduction of imlifidase opens up the possibility of kidney transplantation in highly sensitised patients who would otherwise be crossmatch positive and not eligible for transplantation. Prior to any kidney transplantation, a crossmatch test is performed to assess the risk for acute rejection due to high levels of DSAs. For patients who are highly sensitised, imlifidase can be administered within 24 hours of the transplantation.

Dosing of imlifidase is based on patient body weight (kg). The recommended dose is 0.25 mg/kg administered as a single dose, preferably within 24 hours before transplantation. One dose (2 vials) is adequate for crossmatch conversion in most patients, but if needed, a second dose can be administered within 24 hours after the first dose if a negative crossmatch is not reached with the first dose. Imlifidase is administered intravenously as a single infusion for 15 minutes. Following the administration, it is recommended that patients receive intravenous fluid to ensure administration of the complete dose of imlifidase. In addition to imlifidase, patients will also receive immunosuppressive treatment peri- and post-transplantation (1).

Patients should be monitored for AMR, which may potentially occur as a consequence of rebound of DSA within the first two weeks. Patients with very high levels of DSA before transplantation are somewhat more likely to experience early AMR. The re-appearance of DSAs and increased risk of AMR in highly sensitised patients require physician's previous experience from managing sensitised patients, resources, and preparedness to diagnose and treat acute AMRs according to standard clinical practice. Management of patients should include close monitoring of anti-HLA antibodies, renal function and serum or plasma creatinine monitoring, as well as readiness to perform biopsies when AMR is suspected (1).

Table 4: Imlifidase in Danish clinical practice

	Imlifidase
Generic name(s) (ATC-code)	L04AA41
Mode of action	Imlifidase is a cysteine protease derived from the immunoglobulin G (IgG)-degrading enzyme of Streptococcus pyogenes that cleaves the heavy chains of all human IgG subclasses but no other immunoglobulins. The cleavage of IgG leads to elimination of Fc-dependent effector functions, including CDC, ADCP and ADCC. By cleaving all IgG, imlifidase reduces the level of DSAs, thus enabling transplantation (1).
Pharmaceutical form	Powder for concentrate for solution for infusion (1)

Posology	The dose is based on patient body weight (kg). The recommended dose is 0.25 mg/kg administered as a single dose, preferably within 24 hours before transplantation. If needed, a second dose can be administered within 24 hours after the first dose (1).
Method of administration	Imlifidase is administered intravenously (1).
Dosing	0.25 mg/kg (1).
Should the pharmaceutical be administered with other medicines?	Immunosuppressive therapies will also be administered prior to transplantation (1).
Treatment duration/criteria for end of treatment	Crossmatch conversion (1)
Necessary monitoring, both during administration and during the treatment period	Patients should be monitored for AMR (1).
Need for diagnostics or other tests (i.e., companion diagnostics)	Monitoring of anti-HLA antibodies and serum or plasma creatinine as well as readiness to perform biopsies (1)
Packaging	Imlifidase is supplied as a glass vial containing a powder for concentrate for solution for infusion (powder for concentrate). The powder is a white freeze-dried cake. Each vial contains 11 mg of imlifidase. After reconstitution, each mL of concentrate contains 10 mg imlifidase. Packs contain 1 or 2 vials.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

We conducted three systematic literature searches to identify studies describing the efficacy and safety of imlifidase and dialysis, respectively. To identify efficacy and safety data for imlifidase, we searched for relevant literature in the databases Medline (via PubMed) and Embase (via Ovid) on 3 May 2022, applying relevant Medical Subheadings (MESH) terms and free search terms for imlifidase, the relevant population and prespecified efficacy and safety outcomes. To identify efficacy and safety data for dialysis, we searched for relevant literature in the databases Medline (via PubMed) and CENTRAL (via Cochrane) on 7 July 2022. We applied relevant MESH terms and free search terms for dialysis, the relevant patient population and prespecified efficacy and safety outcomes including survival, QoL and AEs. Detailed information about the systematic searches is provided in Appendix A.

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In general, we included adults with CKD treated with either imlifidase or long-term dialysis. For imlifidase, we searched for meta-analyses, systematic literature reviews, RCTs, non-randomised studies, observational studies, cohort studies, databases and registers, and for dialysis, we searched for meta-analyses and systematic literature reviews. We included studies reporting results on one or more of the predefined efficacy and safety outcomes. Finally, we searched for all English-language literature.

Systematic selection of studies

For studies on imlifidase, we identified 19 records in Embase and 13 records in Medline. A total of 27 records were identified after duplicates were removed. Of these, 20 records were excluded based on title/abstract screening, and an additional three records were excluded based on a full-text assessment, leaving four relevant studies for inclusion in the assessment. The three records that were excluded based on review of the full text are listed in Table 81 (Appendix A), including the reasons for their exclusion.

For studies on AEs with dialysis, we identified three records in CENTRAL and 180 records in Medline. In total, 180 records were identified after removal of duplicates. Of these, 147 records were excluded based on title/abstract screening, and an additional 22 records were excluded based on review at the full-text level, leaving 11 relevant studies for assessment. We assessed the 11 studies based on population size, the population's relevance for CKD patients and whether identification of AEs were a primary aim in the publication to identify the most suitable publication to include as the reference for AEs in PD and HD. Reasons for exclusion at full-text level are presented in Table 88 and Table 89 (Appendix A). In the literature review on survival and QoL, we identified 166 publications. After removing duplicate entries, a total of 158 publications were reviewed. Of these, 145 were excluded on initial review of title and abstract, and nine were excluded at full-text review, leaving one eligible publication with survival data and three eligible publications with relevant HRQoL data. In Table 96 (Appendix A), we have included a list of all records excluded based on review at the full-text level, including reasons for their exclusion.

6.2 List of relevant studies

From the literature reviews, we identified four relevant studies for the assessment of imlifidase, two relevant studies for the assessment of survival in dialysis and one relevant study for the assessment of adverse events in both PD and HD. In addition, the study by Boenink 2020, which was used in a scenario analysis on survival, was identified through dialogue with the DMC. The studies are presented in Table 5.
Additionally, we identified two relevant studies that presented utility values. These are presented in section 8.4.

Moreover, for imlifidase, we identified four relevant ongoing trials listed in Table 77. However, these will not be included in the assessment of imlifidase.

Table 5: Relevant studies in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in the comparison of
Lorant T et al. Safety, immunogenicity, pharmacokinetics, and efficacy of degradation of anti-HLA antibodies by IdeS (imlifidase) in chronic kidney disease patients. Am J Transplant. 2018 (37)	Study 02	NCT02224820	June 2014 to February 2015	Imlifidase
Jordan et al. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation. N Engl J Med. 2017 (38)	Study 03 and Study 04	NCT02475551	June 2015 to October 2016	Imlifidase
Jordan et al. Imlifidase Desensitization in Crossmatch-positive, Highly Sensitized Kidney Transplant Recipients: Results of an International Phase 2 Trial (Highdes). Transplantation. 2021 (39)	Study 06	NCT02790437	June 2016 to July 2018	Imlifidase
Kjellman et al. Outcomes at 3 years posttransplant in imlifidase-desensitized kidney transplant patients. Am J Transplant. 2021 (40)	Study 14	NCT03611621	June 2018 to December 2022	Imlifidase
Chaudhry et al. Survival for waitlisted kidney failure patients receiving transplantation versus remaining on waiting list: systematic review and meta-analysis. BMJ. 2022 (3)	-	-	Database searches were performed from inception until 1 March 2021	Dialysis
Sørensen et al. Survival benefit in renal transplantation despite high comorbidity. Transplantation 2016 (41)	-	-	1 January 1995 to 31 December 2011	Dialysis (sensitivity analysis)
Swai et al. Systematic review and meta-analysis of clinical outcomes comparison between different initial dialysis modalities in end-stage renal disease patients due to lupus nephritis prior to renal transplantation	-	-	28 September 2019	Dialysis
Boenink 2020. Data from the ERA-EDTA Registry were examined for trends in excess mortality in European adults on kidney replacement therapy. Kidney International (7)	-	-	2002 to 2015	Dialysis (scenario analysis)

Note: For detailed information about the included studies, see Appendix B.

7. Efficacy and safety

7.1 Relevant studies

The efficacy and safety of imlifidase were assessed in four phase II studies in patients with ESRD (Studies 02, 03, 04 and 06) and in one long-term (5-year) follow-up study (Study 14) which is ongoing. All patients from the initial feeder studies (n=46) were eligible to participate in Study 14. [redacted] (see Figure 3). In the following sections, we present a pooled analysis of DSA elimination and crossmatch conversion from the four phase II studies. Results on kidney function, graft survival, patient survival and quality of life (QoL) are also presented as well as safety results. In Table 6, an overview of the studies included in the assessment of the efficacy and safety of imlifidase is presented. Please see Appendix B and Appendix C for a detailed description of each study.

Table 6: Overview of Study 02, 03, 04, 06 and Study 14

Study code	Study design	Dosing regimen	Study population	Publication
13-HMedIdeS-02 SE (Study 02)	Open-label, uncontrolled, phase II, single ascending doses. Transplantation not part of protocol (but one patient was transplanted after treatment).	0.12 and 0.25 mg/kg given IV over 15 minutes once or twice within 48 hours	Sensitised patients with ESRD (male and female) on waiting list for transplantation (N=8)	Lorant et al. 2018 (37)
13-HMedIdeS-03 SE (Study 03)	6-month, open-label, uncontrolled, phase II, single dose study to assess safety and efficacy. Transplantation was part of the protocol.	0.25 or 0.5 mg/kg given IV over 15 minutes	Sensitised patients with ESRD (male and female) awaiting deceased donor or living donor transplantation (N= 10)	Jordan et al. 2017 (38)*
14-HMedIdeS-04 US (Study 04)	6-month, open-label, uncontrolled, phase I/II, study with ascending doses. Transplantation was part of the protocol.	0.24 mg/kg given IV over 15 minutes (with the potential to dose escalate to 0.5 mg/kg)	Patients with ESRD, highly sensitised, on the kidney waiting list (N=17)	Jordan et al. 2017 (38)*
15-HMedIdeS-06 US, FR, SE (Study 06)	Open-label, uncontrolled phase II study. Transplantation was part of the protocol.	0.25 mg/kg given IV over 15 minutes with the potential to dose escalate to 0.5 mg/kg	Patients on the kidney waiting list who have previously undergone desensitisation unsuccessfully or in whom effective desensitisation is highly unlikely. Patients have a positive crossmatch	Jordan et al. 2021 (39) and Lonze et al. 2018 (42)

Study code	Study design	Dosing regimen	Study population	Publication
			against available donor (N=19).	
17-HMedIdeS-14 US, FR, SE (Study 14)	Prospective, observational long-term follow-up study of patients treated with imlifidase prior to kidney transplantation in previous studies	N/A	Patients with ESRD exposed to imlifidase in Studies 02, 03, 04 or 06. (N = up to 43)	Kjellman et al. 2021 (40)

*Study 03 and Study 04 are both published in Jordan et al. 2017 (38).

7.1.1 Description of Study 02, 03, 04 and 06

Study 02, 03, 04 and 06 (13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06) were all phase II, open-label, single-arm studies evaluating the dosing regimen, efficacy, and safety of imlifidase as pre-transplant treatment to reduce donor-specific IgG and enable highly sensitised transplant candidates to be eligible for kidney transplantation (in Study 02, transplantation was not part of the protocol, but one patient received a donor offer after imlifidase treatment and was transplanted. This patient was included in the pooled analysis). An overview of the study design is presented in Figure 2.

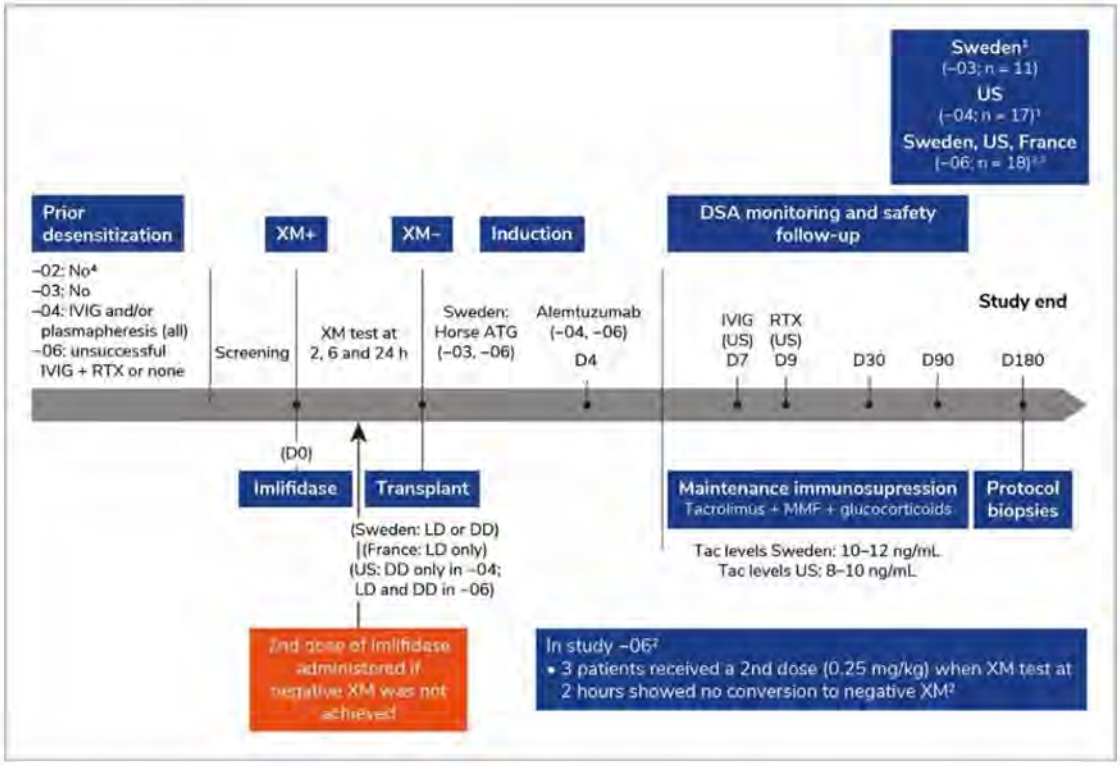

Figure 2: Study design of Study 02, 03, 04 and 06

Note: Horse ATG (ATGAM) was administered at day 1 till 4. Pulse steroids were given from day 1-4 in case alemtuzumab was used as induction. Abbreviations: ATG, anti-thymocyte globulin; DD, deceased donor; DSA, donor-specific antibodies; IVIg, intravenous immunoglobulin G; LD, living donor; MMF, mycophenolate mofetil; RTX, rituximab; Tac, tacrolimus; XM, crossmatch. In Study 04, [redacted] US patients received IVIG and rituximab prior to imlifidase treatment.

46 highly sensitised patients, all diagnosed with ESRD and on dialysis, were treated with imlifidase and subsequently transplanted within the studies. Patients were between 20 and 73 years of age, and the mean age of the study population was similar for Study 02 and Study 03 (50.5 years and 51.6 years, respectively), while the mean age of the study population was similar for Study 04 and Study 06 (41.3 years and 39.1 years, respectively). There was a total of 21 (46%) women and 25 (54%) men in the studies. All patients were sensitised, 41 (89%) were highly sensitised (cPRA ≥ 80%), 33 (72%) of whom had a cPRA ≥ 95%.

All phase II studies were open-label uncontrolled studies. Study 02 and 03 were studies with ascending dose, and in Study 04 and Study 06, if XM conversion was not achieved, a second dose could be given within 24 hours of the first dose. In Study 02, the starting dose of imlifidase was 0.12 mg/kg given by intravenous (IV) infusion over 15 minutes once or twice. The second dose group received one or two doses of 0.25 mg/kg or less. In Study 03 and 06, the starting dose of imlifidase was 0.25 mg/kg given IV over 15 minutes. In Study 03, the dose was given once. After evaluation of the safety and efficacy in the first dose group, the second dose group received one dose of 0.50 mg/kg or less. Dose escalation was decided by a data monitoring committee or board in all three studies. Study 04 was a single-dose study in which the starting dose was 0.24 mg/kg given on day 0. All phase II studies expect Study 02 had a total follow-up of 180 days (6 months). Study 02 had a total follow-up of 64 days. Please see Appendix C for a detailed overview of the baseline characteristics of patients in the studies.

Table 7: Pooled patient characteristics of the four phase II studies

Patient Characteristics	Total N=46
No. of previous transplants	
0	14 (30%)
1	24 (52%)
2	6 (13%)
3	2 (4%)
cPRA (%) (MFI cut-off: 3000)	
<80%	6 (13%)
80-94.9	8 (17%)
95-97.4	4 (9%)
97.5-98.4	0
98.5-99.4	5 (11%)
99.5-100	23 (50%)
Any crossmatch positivity, n (%)	39 (85%)

The overall primary efficacy endpoint in Study 02, 04, and 06, as well as the first secondary endpoint in Study 03, was the ability of imlifidase to decrease the anti-HLA antibody level and, if present, convert a positive crossmatch to negative within 24 hours to make the patient immediately eligible for kidney transplantation. The endpoints were slightly differently phrased in the studies (see Table 8); in Study 02 and Study 03, a general decrease in the read-out of MFI values in the SAB-HLA assay was specified. In Study 04, the number and levels of DSA were specified, while in Study 06, the primary endpoint was defined as creation of a negative crossmatch. Study 02 and Study 03 investigated different dose regimens to obtain the desensitisation, in Study 02 without planning for actual transplantation, while in Study 03, Study 04, and Study 06, transplantation was part of the protocol.

Table 8: Overview of outcomes and definitions from Study 02, 03, 04, 06 and Study 14 used for efficacy evaluations in the current application. Sources: clinical study reports (CSRs) on the trials.

	Outcome used in pooled analyses
Study 02	**Primary endpoint: IdeS dosing scheme resulting in HLA antibody levels which are acceptable for transplantation** Definition/method of analysis: measured as an MFI of less than 1100 as measured in an SAB assay, within 24 hours from dosing. The primary endpoint was analysed by selecting all pre-dose MFI values >1100 which had the 90th percentile MFI <1100 within 24 hours after IdeS treatment.
Study 03	**Secondary endpoint: IdeS dosing scheme resulting in HLA antibody levels acceptable for transplantation within 24 hours from dosing** Definition/method of analysis: anti-HLA antibodies were analysed in IgG single antigen solid-phase immunoassay for antibodies to HLA class I and class II (SAB-HLA). The assay allows determination of the strength of individual HLA antibodies in patient serum reacting to an array of individual HLAs immobilised to beads. The SAB-HLA analyses were performed using the commercial assay LABScreen® Single Antigen (One Lambda [a Thermo Fisher Scientific brand], CA, USA). **Secondary endpoint: Kidney function in patients who were transplanted** Definition/method of analysis: kidney function was evaluated by the following parameters: creatinine, estimated eGFR and kidney biopsy findings. eGFR is presented in the current application. The eGFR was calculated as: eGFR (mL/min/1.73 m^2) = 175 × (s-creatinine) - 1.154 × (age) - 0.203 × (0.742 if female) × (1.212 if African American) (43).
Study 04	**Primary endpoint: DSA levels pre- and post-transplantation** Definition/method of analysis: defined as antibodies directed against donor HLA measured in the SAB-HLA assay and with an MFI value >2000. DSAs were identified based on donor and recipient HLA types for each patient-donor pair. **Primary endpoint: Kidney function** Definition/method of analysis: assessed by eGFR throughout the study and estimated using the Modification of Diet in Renal Disease (MDRD) equation.
Study 06	**Primary endpoint: Ability of imlifidase to convert a positive crossmatch (CXM) to a negative within 24 hours after dosing** Definition/method of analysis: analysed using CXM tests. The pre-dose analyses were performed for all patients, while all post-dose CXM tests were not performed for all patients. For most of the patients, the tests at 2 and 6 hours were analysed, and if one or both were negative, the patient proceeded to transplantation and no more CXM tests were performed. CXM tests were performed at the local laboratories according to standard practice at each local laboratory. **Secondary endpoints: DSA levels at pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180 post-imlifidase treatment** Definition/method of analysis: samples for determination of DSAs were analysed in single antigen bead (SAB) solid-phase assay for antibodies to HLA class I and class II. LABScreen Single Antigen HLA Class I (LS1A04) and LABScreen Single Antigen HLA Class II (LS2A01) from One Lambda were used for all samples. The assay allowed determination of the MFI of antibodies in patient serum reacting to an array of individual HLA immobilised to beads.

	Outcome used in pooled analyses
	Kidney function after imlifidase treatment assessed by filtration (eGFR) up to 180 days post treatment Definition/method of analysis: evaluation of kidney function was performed based calculation of the eGFR. The eGFR was calculated as described in the MDRD equation: eGFR (mL/min/1.73 m^2) = 175 × (s-creatinine)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American) (43).
Study 14	**Primary endpoint: Graft survival** Definition/method of analysis: time from transplantation to graft loss at 1, 2, 3 and 5 years after first dose of imlifidase. Graft loss is defined as permanent return to dialysis for at least six weeks, re-transplantation, or transplantectomy. If dialysis was used to define graft loss, the date of graft loss was the first day of the last ongoing dialysis period reported. **Secondary endpoint: Overall patient survival** Definition/method of analysis: time from transplantation to death for any cause.

7.1.2 Description of Study 14

Study 14 is a phase II, prospective, observational, long-term (5-year) follow-up study currently with 3 years of follow-up data (2). The trial included patients treated with imlifidase prior to kidney transplantation from Studies 02, 03, 04 and 06, i.e., the "feeder studies". Any patient is assessed at each year-passage, i.e., patients with 3-year data are also assessed at 1 and 2 years (2).

The study can include up to 46 patients who will be assessed by kidney function, graft survival, quality of life and patient survival for 5 years. At the data cut-off in February 2021, enrolment was expected to be completed, and as seen in Figure 3 [redacted] are presented as agreed by the respective independent ethics committee (IEC) or institutional review board (IRB). The full analysis set (FAS) is defined as all patients enrolled [redacted] Because of the non-interventional nature of this study, no other analysis set was defined, and all data presentations and analyses are based on the FAS.

The study primarily determined the time of graft survival in subjects who have received imlifidase prior to kidney transplantation. The subjects are planned to attend up to 4 follow-up visits 1, 2, 3 and 5 years after imlifidase administration. Some subjects did not perform all 4 visits because the study start was after the subjects' first visit(s) should have taken place. An overview of the subject disposition is presented in [redacted], and the disposition of follow-up visits is presented in [redacted].

7.2 Efficacy results

7.2.1 Pooled analysis from Study 02, 03, 04 and 06 on DSA elimination and crossmatch conversion

An outcome in many of the imlifidase studies was the ability of imlifidase to remove DSAs and thereby convert a positive CXM test into a negative. The FCXM and CDCXM tests were applied (see Table 10). The results for this outcome are presented from a pooled analysis. The rationale behind pooling the results from the four phase II studies was the small patient numbers included in each trial. Pooling of the results was found to be acceptable given the

similar study designs, follow-up times, patient characteristics of the phase II studies and outcome definitions. The pooled analysis was on 46 patients from Study 02 (one patient), Study 03 (10 patients), Study 04 (17 patients) and Study 06 (18 patients). The definitions of each outcome from each study have been presented in Table 8, and the comparability of the studies was described in section 7.1.

Table 10: Crossmatch, pre-dose (safety set, transplanted). Source: EPAR on imlifidase (2)

Crossmatch			T-cells Negative	Positive	Missing	Total
FCXM	B-cells	Negative	7 (15.2%)	2 (4.3%)	-	9 (19.6%)
		Positive	22 (47.8%)	14 (30.4%)	-	36 (78.3%)
		Missing	-	1 (2.2%)	-	1 (2.2%)
CDCXM	B-cells	Negative	11 (23.9%)	-	-	11 (23.9%)
		Positive	7 (15.2%)	3 (6.5%)	-	10 (21.7%)
		Missing	2 (4.3%	-	23 (50.0%)	25 (54.3%)

Crossmatch (XM) conversion was achieved by the end of the studies in all patients who received imlifidase, generally within a few hours. The crossmatch conversion was confirmed by DSA analysis (CDCXM and FCXM), which showed that, across all studies, imlifidase rapidly and significantly decreased the number of anti-HLA antibodies with MFI >3000 in all patients, making them eligible for transplantation within the designated time frame, and subsequently, all participants received a transplant. Figure 4 presents an overview of DSA elimination from Study 06.

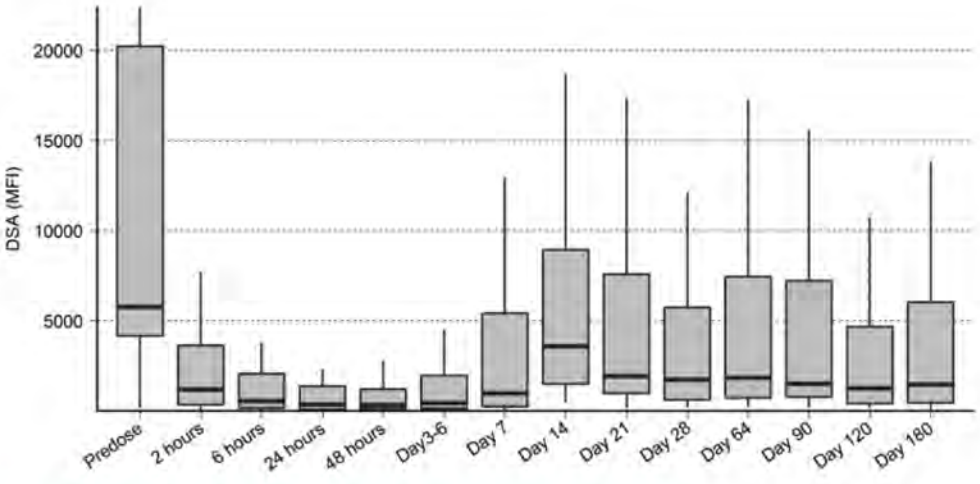

Figure 4: Dynamics of DSAs after imlifidase treatment from Study 06

Note: The horizontal line in the boxes shows the median, the top and bottom of the boxes the interquartile range, and the bars the range of values excluding potential outliers more than 1.5 x Interquartile range (IQR) off the box. The dotted line is the MFI 3000 cut-off. Source: Jordan et al. 2020 (39).

In [redacted], we present the median DSA levels at different time periods and the 25% and 75% quartiles. [redacted]

[redacted]

7.2.1 Kidney function

eGFR calculated from serum creatinine was used as an outcome measure for kidney function and was assessed for all transplanted patients with a functioning kidney (data from the patient in Study 02 not available). [redacted]

[redacted]

[redacted]

[redacted]

[redacted] presents the mean and standard errors (SE) presented in [redacted] as well as standard deviations (SD) and mean differences in eGFR compared to eGFR pre-dose. [redacted]

[redacted]

[redacted]

7.2.1 Overall graft survival from Study 14

In Study 14, the primary outcome was overall graft survival defined as time from transplantation to graft loss evaluated at 1, 2, 3 and 5 years after first dose of imlifidase. Graft loss was defined as permanent return to dialysis for at least 6 weeks, re-transplantation or transplantectomy. If dialysis was used to define graft loss, the date of graft loss was the first day of the last ongoing dialysis period reported.

The outcome was analysed with the Kaplan-Meier survival method. The following events were censored at the time of occurrence: withdrawal from the study without graft loss, death not caused by graft loss, evaluation time point (the yearly evaluations) and end of study without graft loss. The Kaplan-Meier analysis in this study was not comparative because of the non-interventional nature of the study. Hence, there is no formal statistical hypothesis or testing.

[redacted]

[redacted]

[redacted]

7.2.2 Overall patient survival Study 14

Overall, patient survival is defined as time from transplantation to death for any cause evaluated at 1, 2, 3 and 5 years. The outcome was analysed the same way as the primary endpoint (graft survival). The following events were censored: withdrawal from the study, evaluation time point (the yearly evaluations), and end of study.

[redacted]

[redacted]

[redacted] (44).

7.2.3 Quality of life results from Study 14

Quality of life (QoL) was assessed in Study 14 with the specific kidney disease-related Kidney Disease Quality of Life-Short Form (KDQOL-SF version 1.3). No QoL data was available in the four feeder studies, and no pre-transplantation data was available. QoL outcomes were first measured in the follow-up studies at 1 year or more post-transplantation.

KDQOL-SF includes 43 kidney disease-targeted items such as the effects of the disease on activities of daily living, work status and social interaction, 36 items that provide a measure of physical and mental health, and one overall health rating item ranging from 0 ("worst possible health") to 10 ("best possible health.") (46). The questionnaire was answered at all visits (1, 2, 3 and 5 years). Scores of different subscales were calculated according to the KDQOL-36 scoring program. Values for each item were transformed linearly to a 0 to 100 range, with higher scores reflecting better quality of life.

Results are presented in [redacted]

[redacted]

7.3 Safety results

7.3.1 Adverse events and serious adverse events

In most studies, an AE was defined as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Relationship to the study drug was deemed as not related, unlikely, possible or probable. The term AE was used to include both serious and non-serious AEs.

A SAE was in most studies defined as an AE occurring during any study phase (i.e., run-in, treatment, washout and follow-up) and fulfilled one or more of the following criteria:

- Resulted in death
- Was immediately life-threatening
- Required in-patient hospitalisation or prolongation of existing hospitalization. Regular dialysis treatment in or outside hospital was not included.
    - Hospitalisation for transplantation was not considered an SAE.
- Resulted in persistent of significant disability or incapacity
- Was a congenital abnormality or birth defect
- Was an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

The total number of patients in Study 02, 03, 04 and 06 was 54, and 46 patients underwent transplantation. Information on the 54 patients is provided in Table 16. As seen in Table 16, five of the 54 patients with CKD did not complete their study (49 out of 54 completed the core study).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3.2 Antibody-Mediated Rejection (AMR)

7.3.2.1 Adjudication process and adjudication criteria

Hansa Biopharma adjudicated all potential AMRs reported as AEs and AMRs found at the protocol-defined routine biopsy taken at month 5-6. Evaluations were based on the Banff 2017 criteria (47). The adjudication was unblinded, consistent with the studies being uncontrolled. At the adjudication, the following criteria had to be fulfilled to constitute an AMR:

- a biopsy was taken at the time of the AMR;
- histological evidence of an AMR was reported in the pathology report; and
- presence of detectable levels of DSAs and/or evidence of antibody-mediated morphological changes in the kidney transplant at the time of the biopsy.

AMRs identified by biopsy with clinical supporting evidence, e.g., data on kidney function, were adjudicated as "active and/or chronic AMR" (for definition see Haas et al. 2018 (47)), and AMRs indicated by biopsy, but with the absence of clinical supporting evidence, were adjudicated as "subclinical AMR".

An acute rejection episode is the consequence of an immune response of the host attacking the transplanted organ or cells. The response can be of cellular (primarily T lymphocytes) (CMR) and/or humoral (circulating HLA and non-HLA antibodies) (AMR) origin. An acute rejection is clinically suspected in patients with an increase in serum creatinine or increased proteinuria after the exclusion of other causes of graft dysfunction, and the diagnosis is generally confirmed by biopsy. 15/46 (33%) subjects had at least one episode of antibody-mediated changes including the hyperacute IgM antibody-mediated rejection in one subject. Of the 46 subjects, 31 (67%) did not have any signs of AMR.

12 (26%) of the 45 successfully transplanted subjects experienced AMRs that were biopsy-proven combined with clinical signs and defined as active and/or chronic, while two (4%) subjects had AMRs that were identified at a biopsy without any clinical signs and defined as subclinical. The AMR incidence was similar to what is reported in the literature for crossmatch-positive desensitised kidney transplant recipients (48–51). Results are summarised in Table 19.

Table 19: Number and proportion of patients with AMR. Source: EPAR (2).

	Study 02 N=1	Study 03 N=10	Study 04 N=17	Study 06 N=18	Total N=46
	n (%)	n (%)	n (%)	n (%)	n (%)
Active/chronic AMR	0 (0%, 95% CI: not applicable)	3 (30%, 95% CI: [redacted]	2 (12%, 95% CI: [redacted]	6 (33%, 95% CI: [redacted]	12 (26%, 95% CI: [redacted]
Subclinical AMR	0 (0%, 95% CI: not applicable)	0 (0%, 95% CI: [redacted]	1 (6%, 95% CI: [redacted]	2 (11%, [redacted]	2 (4%, 95% CI: [redacted]
Hyperacute rejection	0 (0%, 95% CI: not applicable)	0 (0%, 95% CI: [redacted]	1 (6%, 95% CI: [redacted]	0 (0%, 95% CI: [redacted]	1 (2%, 95% CI: [redacted]

*Confidence intervals calculated by dividing 3/n as suggested by the Cochrane handbook (version 5.1.0 (45)).

**Confidence intervals calculated with Clopper-Pearson's exact method.

7.4 Comparative analyses of efficacy and safety

No comparative analyses of efficacy and safety are presented in the current application, as no appropriate comparators are currently available for desensitisation treatment for highly sensitised patients with ESRD awaiting a kidney transplantation in Denmark. In addition, all imlifidase studies are single-arm studies including desensitisation-related and transplantation-related outcomes, which will not be included as outcomes in any potential standard of care studies.

8. Health economic analysis

The health economic analysis conducted in the present application is a cost-utility (CU) analysis. The purpose of the health economic analysis was to provide a meaningful comparison of imlifidase vs the current best supportive care for Danish patients with ESRD. Specifically, this was analysed by estimating the cost per incremental QALY in for patients treated with imlifidase and receiving subsequent kidney transplantation as compared to patients who cannot be transplanted and receives dialysis therapy as best supportive care. The analysis was based on a global CU model adjusted to a Danish setting.

8.1 Model

8.1.1 Model structure

The model consists of three health states: 1) dialysis (haemodialysis, home haemodialysis, or peritoneal dialysis), 2) functioning graft and 3) death. Figure 8 illustrates the model structure of the CU analysis.

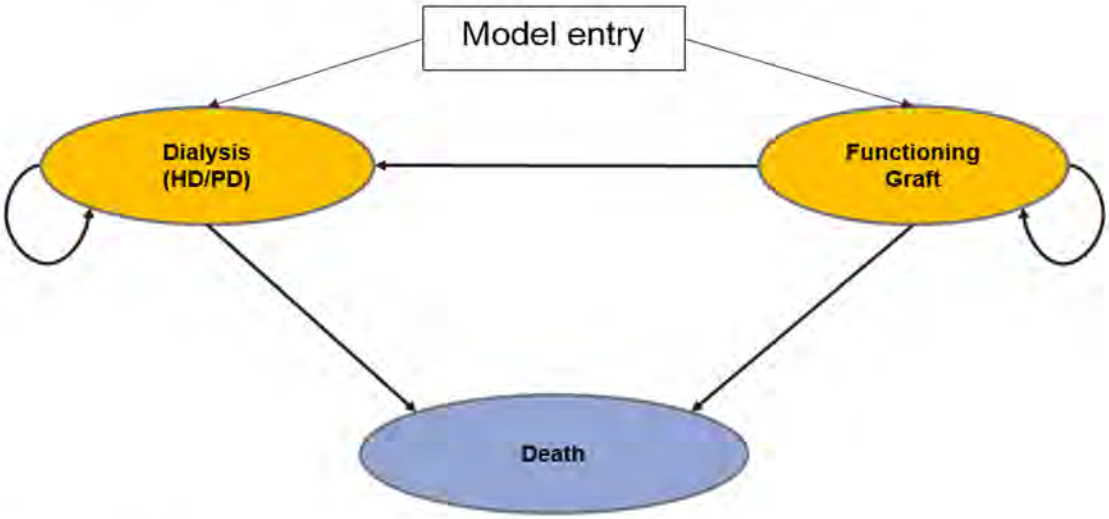

Figure 8: model structure

8.1.2 Patient flow in the model

As the target population is highly sensitised patients that are unlikely to be transplanted under the available kidney allocation system, the patient cohort enters the model in one of two ways: 1) patients that are not treated with imlifidase and enter the model on dialysis. Dialysis represents the current best supportive care in Denmark. The majority of patients who enter the model on dialysis will not receive a kidney transplant; however, to reflect Danish clinical practice, a small percentage of patients in the dialysis arm received a transplantation within the first two years in the model. The percentage of patients transplanted in the dialysis arm is a function of how "unlikely to be transplanted" is interpreted. In conversations with Danish clinicians, they have identified a very specific highly sensitised crossmatch-positive patient population that does not have any other opportunities for a kidney transplant. The extremely low probability of receiving a compatible organ means that it could still theoretically occur for this type of patient, but the odds of these 6–8 patients getting transplanted without imlifidase in Denmark are so small that it is in reality close to 0%, but 2% per year the first two years was assumed in the base case. The assumption of 2% within the first two years was based on the fact that the probability of a transplant becomes much lower if patients remain

on the STAMP and LAMP waiting lists for more than two years. The remaining continued receiving dialysis until death. 2) patients can be treated with imlifidase, which converts a positive crossmatch to negative crossmatch and thereby enables transplantation of an otherwise HLA-incompatible kidney. Patients who undergo transplantation will remain in the 'functioning graft' health state until they lose their graft and transition to dialysis therapy. Patients who lose their graft cannot regain it (as imlifidase cannot be used for more than one transplantation) and will remain on dialysis until death. After each model cycle, patients can either stay in the same state or progress to a new health state.

Note: Given the rapid and extensive development of anti-imlifidase antibodies and associated toxicity after repeated administrations, imlifidase cannot be used for more than one transplantation. This is specified in the SMPC for imlifidase (1).

8.1.3 Model assumptions

The model includes the following assumptions:

- Treatment with imlifidase achieves 100% efficacy in converting the positive crossmatch into a negative crossmatch (including re-dosed patients).
- The target population includes only patients who are on renal replacement therapy (RRT) and in need of a kidney transplant and who are unable to receive a DD transplant without treatment with imlifidase. However, we have assumed that 2% in the dialysis arm are transplanted per year the first two years. In the absence of imlifidase, the only available treatment option is dialysis, and the remaining patients stay on dialysis until they die.
- Imlifidase treatment may only be used for one transplant per patient; thus, re-transplants with the use of imlifidase are not possible.

8.1.4 Applied perspective

The base case model has a limited societal perspective in accordance with DMC guidelines (52). This means that all relevant hospital-related costs, costs covered by public health services, treatment-related costs incurred by the patient and municipal costs are included. Relevant transport costs and time spent by patients are also included. The health effects for patients are estimated based on the expected lifetime of patients and health-related quality of life (HRQoL).

8.1.5 Time horizon and cycle length

The model has a user-defined time horizon. The time horizon of the base case simulation corresponds to a patient's lifetime, due to the chronic nature of the disease. In the model, the time horizon is set to 57 years, corresponding to 114 model cycles. Shorter time horizons of 10 and 20 years are considered in the scenario analysis. The simulation is conducted in cycles of six months over a lifetime time horizon. The choice of cycle duration is based on the consideration that clinically meaningful events typically happen in this disease within six months of treatment. For example, a clinical event such as AMR typically happens in the first six months (40) . A half-cycle correction was applied.

8.1.6 Discounting

Both costs and QALY were discounted at a rate of 3.5%, in line with the Danish Ministry of Finance (53) and the DMC guidelines (52). The guidelines stipulate that costs in years 36-70 should be discounted by 2.5% per annum. This discounting is implemented by subtracting 1 percentage point from the discount rate in year 36-57.

8.1.7 General mortality

General population background mortality was implemented using the most recent National Life Tables for Denmark (Statistics Denmark, Table HISB8 (54)).

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

In Table 20, we present input data on clinical efficacy, adverse reactions and health state utility values (HSUVs) applied in the model and describe how these input data were obtained.

Table 20: Input data used in the model

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the base case model	How the input value is obtained/estimated
Initial age*	[redacted]	[redacted]	Baseline characteristics were based on patient characteristics from imlifidase study 02, 03, 04, and 06 (data on file (55)) (Appendix C).
Proportion of females (%)*	[redacted]	[redacted]	The proportion of females was based on patient imlifidase study 02, 03, 04, and 06 (data on file (55)) (Appendix C).
Graft survival	Results from Study 14 on overall graft survival is presented in Table 13, and Kaplan-Meier curve is presented in Figure 6. Three out of 46 patients experienced graft loss within the first six months of the trial [redacted]	Data with three years follow up were applied to extrapolate data time to allograft loss (55). [redacted]	Data on time to allograft loss was used to extrapolate graft survival beyond the study period. The exponential function provided the best fit for the estimated graft survival.

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the base case model	How the input value is obtained/estimated
Patient survival with a functioning graft	Results from Study 14 on overall patient survival are presented in Table 14, and a Kaplan-Meier graph is presented in Figure 7. [redacted]	Data with three years follow up were applied to extrapolate survival with functioning graft (55). [redacted]	Data from all 46 patients who underwent a kidney transplant studied within the imlifidase clinical trials was used to estimate the survival with a functioning graft. Patients were censored when they lost their graft, and only survival with a functioning graft was considered in the predicted survival. An exponential function provided the best fit for the survival.
Dialysis survival	Chaudhry et al. 2022 (3) was identified in the SLR and investigate the survival benefit of transplantation versus dialysis for patients who have undergone renal transplantation versus patients who are on dialysis and are on waiting list for a transplant. The hazard ratio (HR) for long-term, all-cause mortality in the transplantation group compared with the dialysis group was 0.49. Through Chaudhry et al. 2022 (3), we identified Sørensen et al. 2016 (41), who merged data from the Danish Nephrology Registry and Scandiatransplant to evaluate the effect of transplant on overall survival. The study found that receiving deceased donor transplant significantly reduced the risk of death (HR = 0.38). We apply these estimates in a sensitivity analysis.	The reciprocal value of the HR for long-term, all-cause mortality in the transplantation group compared with the dialysis group was applied in the model in the base case, HR = 2.04.	The input value is the mortality hazard rate for transplantation vs dialysis.

<table>
<tr><th>Name of estimates*</th><th>Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)</th><th>Input value used in the base case model</th><th>How the input value is obtained/estimated</th></tr>
<tr><td>Baseline utility</td><td>Lee et al. 2005 (56) assessed the HRQoL using EQ-5D for 382 patients receiving either HD, PD or renal transplant.

Treatment | HSUV
Haemodialysis | 0.44
Peritoneal dialysis | 0.53
Transplanted patient with functioning graft | 0.71

In addition to Lee et al. 2005, we identified the Eriksson et al. 2017 publication, in which HRQoL was assessed with EQ-5D in 124 patients receiving either transplant or dialysis.

Treatment | HSUV
Dialysis | 0.73
Transplanted patient with functioning graft | 0.85</td><td>Health state utility values in the model were based on age-adjusted utility values from Lee et al. 2005 (56).

Treatment | HSUV
Haemodialysis | 0.44
Peritoneal dialysis | 0.53
Transplanted patient with functioning graft | 0.71</td><td>Health state utility values in the model were calculated based on Lee et al. 2008 (56).

Danish age-specific EQ-5D-3L utility scores from the DMC guideline on age adjustment of health-related quality of life was used in the model (57).</td></tr>
</table>

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the base case model	How the input value is obtained/estimated
Imlifidase-related AEs	The following data on SAEs related to treatment with imlifidase is based on the EPAR for imlifidase (2). **Adverse event** / **%** Pneumonia 5.6% Sepsis 3.7% Abdominal infection 1.9% Catheter site infection 1.9% Parvovirus infection 1.9% Upper respiratory tract infection 1.9% Infusion-related reaction 1.9% Myalgia 1.9%	Risk of AEs in cycle 1: **Adverse event** / **%** Pneumonia 5.6% Sepsis 3.7% Abdominal infection 1.9% Catheter site infection 1.9% Parvovirus infection 1.9% Upper respiratory tract infection 1.9% Infusion-related reaction 1.9% Myalgia 1.9%	The model includes SAEs related to treatment with imlifidase (cycle 1) based on the EPAR for imlifidase (2)
Transplant-related AEs	The following data on transplant-related adverse events is based on data from study 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06 (55). **Adverse event** / **%** AMR, 0-6 months [redacted] AMR, 6-12 months [redacted] Delayed graft function (Cycle 1) [redacted]	The model includes transplant-related adverse events based on data from study 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06 (55) **Adverse event** / **%** AMR (Cycle 1) [redacted] AMR (Cycle 2) [redacted] Delayed graft function (Cycle 1) [redacted]	Transplant-related AEs including AMR and delayed graft function from study 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS- 04 and 15-HMedIdeS-06 (55). In these studies, no AMR events were reported after the first year. These data were used to inform the model probability of AMR in the first and second cycle of the model.

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the base case model	How the input value is obtained/estimated
Dialysis AEs	The dialysis-related AE parameters used in the model are based on estimates from Swai et al. (58,59). **Adverse event** — **%** All-cause infections (PD patients) — 8.1% All-cause cardiovascular events (PD patients) — 13.0% All-cause infections (HD patients) — 13.1% All-cause cardiovascular events (HD patients) — 13.6%	Risk of AEs per cycle (6 months): **Adverse event** — **%** All-cause infections (PD patients) — 8.1% All-cause cardiovascular events (PD patients) — 13.0% All-cause infections (HD patients) — 13.1% All-cause cardiovascular events (HD patients) — 13.6%	The dialysis-related AE parameters used in the model are based on estimates from Swai et al. (59)
Imlifidase treatment distribution	Weight distributions were derived from weight data of the combined patient populations for Study 02, Study 03, Study 04 and Study 06 (55).	**Dose of imlifidase:** [redacted]	The proportion of patients requiring one, two or three vials were based on the baseline weight of the combined patient populations for study 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS- 04 and 15-HMedIdeS-06. The proportion of patients requiring a second dose was based on the number of patients who had a positive crossmatch after the first dose and thus required a second dose.

*Some of these estimates will be presented in other tables in the document. This table is a summary.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The Danish patient population

Danish adult patients (≥18 years) with ESRD who are awaiting kidney transplantation and are considered highly sensitised due to their broad anti-HLA antibody profile leaving them unlikely to receive a compatible donor organ through the local or Scandiatransplant allocation programmes, including the priority programmes (STAMP and/or LAMP).

In Denmark, approximately 44 patients are active on the STAMP waiting list (with a transplantability score ≤2%). Of these, 15 patients have a transplantability score ≤0.05, and of these, 10 patients have a score = 0.00. These patients have no living donor, and inactivation of anti-HLA antibodies by imlifidase would enable DD transplantation with an HLA-incompatible organ.

Baseline characteristics of patients treated with imlifidase in the clinical trials, were presented to the clinical expert during an in-depth interview. The clinical expert agreed that the baseline characteristics were representable of what would be expected to be the case in the Danish patient population, although the clinical expert noted that the share of females and the share of patients with a body weight of more than 88 kg is expected to be slightly higher in Danish clinical practice. Specifically, the clinical expert stated that it was expected that around 60% of patients with ESRD and who are highly sensitised are female, and that approximately 20% of patients would be expected to weigh more than 88 kg. We asses these potential deviances in demographic characteristics between the population studied in the clinical trials and the Danish patient population as having minimal impact on clinical endpoints as well as the cost-effectiveness of imlifidase. In section 8.7, we present results from the sensitivity analysis where we account for the deviances.

Patient population in the clinical documentation submitted

The patient population in the clinical documentation is presented in Appendix C.

Patient population in the health economic analysis submitted

The model was developed to reflect Danish adult patients with ESRD on the kidney transplant waiting list who are highly sensitised with anti-HLA antibodies and unlikely to be transplanted under the available kidney allocation system, including a prioritisation programme for highly sensitised patients, with positive crossmatch with a DD kidney. Table 21 summarises the patient population in the clinical documentation, data used in the model and the Danish clinical practice.

Table 21: Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc.	Used in the model	Danish clinical practice
Mean age	[redacted]	[redacted]	Approx. 45 years (Danish clinical expert (60))
Share females	[redacted]	[redacted]	Approx. 60% (Danish clinical expert (60))
Weight distribution	[redacted]	[redacted]	≤44 kg: 3.7% 44-88 kg: 76.3% ≥88 kg: 20.0% (Danish clinical expert (60))

8.2.2.2 Intervention: imlifidase

Imlifidase is the first approved treatment for desensitisation of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor in Denmark. A description of how imlifidase is expected to be used in Danish clinical practice can be found in section 5.

Intervention in the clinical documentation submitted

The posology for the intervention in the clinical documentation is presented in Table 4 and Table 22.

Intervention as in the health economic analysis submitted

The model base case considers a weight-based dose administration and related costs for imlifidase. One vial is considered for patients with a weight ≤44 kg, two vials for those who weigh between 44–88 kg, and three vials for patients who weigh ≥88 kg. The proportion of patients requiring one, two or three vials was based on the baseline weights of the combined patient populations for Study 02, Study 03, Study 04, and Study 06 (55).

Table 22: Imlifidase

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	See Table 20	[redacted]	See Table 20 and section 5.

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
The pharmaceutical's position in Danish clinical practice	If recommended, imlifidase will be the only available treatment for desensitisation of highly sensitised patients waiting for a DD kidney transplant.		

8.2.2.3 Comparators

The current Danish clinical practice (as described in section 5.2):
In Denmark, there are currently no alternative treatment option for desensitisation of highly sensitised patients with ESRD and a positive crossmatch against an available deceased donor, and these patients are not kidney transplanted today. Instead, patients will receive best supportive care, which in Denmark consist of HD and PD dialysis. Hence, dialysis is the established best supportive care for the specified patient population without imlifidase.

As there are currently no appropriate comparators available for desensitisation treatment for highly sensitised patients with ESRD awaiting kidney transplantation in Denmark, the choice of comparator has been discussed with the DMC at the dialogue meeting. In the health economic model, the comparison will be conducted with the current best supportive care for these patients: HD and PD dialysis. However, no data on efficacy and safety was presented in the clinical documentation.

Table 23: Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	N/A	Based on statements from the clinical expert, patients receive treatment with the following frequencies: **Treatments per year:** In-centre haemodialysis: 156 Home haemodialysis: 208 Peritoneal dialysis: 364	Based on statements from the clinical expert, patients receive treatment with the following frequencies: In-centre haemodialysis: 156 Home haemodialysis: 208 Peritoneal dialysis: 364
Length of treatment	N/A	Treatment is ongoing until death.	Treatment is ongoing until death.
The comparator's position in Danish clinical practice	N/A	Standard of care and the only available treatment. Patients will continue dialysis treatment until death.	

8.2.2.4 Relative efficacy outcomes

No estimates of the relative efficacy were presented from the clinical documentation (see rationale in section 7.4). Instead, the allograft survival and survival with a functioning graft were based on extrapolation of data from all 46 patients within the imlifidase clinical trials who underwent a kidney transplant. Patients were censored when they lost their graft, and only survival with a functioning graft was considered in the predicted survival. An exponential function provided the best fit for the survival.

Table 24: Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Graft survival	Results from Study 14 on overall graft survival is presented in Table 13, and Kaplan-Meier curve is presented in Figure 6. Three out of 46 patients experienced graft loss within the first six months of the trial and three out of 31 patients experienced graft loss between years two and three. [redacted]	[redacted]
Patient survival with a functioning graft	Results from Study 14 on overall patient survival are presented in Table 14, and a Kaplan-Meier graph is presented in Figure 7. Three out of 36 patients died between six months and one year follow-up. [redacted]	[redacted]
Dialysis survival	Chaudhry et al. 2022 (3) investigated the survival benefit of transplantation versus dialysis for patients who have undergone renal transplantation versus patients who are on dialysis and are on waiting list for a transplant. The HR for long-term, all-cause mortality in the transplantation group compared with the dialysis group was 0.49.	The reciprocal value of the HR for long-term, all-cause mortality in the transplantation group compared with the dialysis group was applied in the model, HR = 2.04.

Table 25: Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Graft survival	Data from all 46 patients who underwent a kidney transplant studied within the imlifidase clinical trials was used to estimate the allograft survival. An exponential function provided the best fit for the survival.	Allograft survival serves as a key endpoint of interest in Danish clinical practice.	N/A
Patient survival with a functioning graft	Data from all 46 patients who underwent a kidney transplant studied within the imlifidase clinical trials was used to estimate the survival for patients with a functioning graft. An exponential function provided the best fit for the survival.	Patient survival with a functioning graft serves as a key endpoint of interest in Danish clinical practice.	N/A
Dialysis survival	Chaudhry et al. 2022 (3) was a systematic literature review that included 14 observational studies with European populations. Data from all 14 studies have been weighted accordingly and are included in the pooled HR estimate.	Overall survival for patients receiving dialysis treatment serves as a key endpoint of interest in Danish clinical practice.	N/A

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes associated with imlifidase and subsequent transplantation are presented in section 7.3. Adverse events associated with dialysis were based on the findings from a systematic literature search. The details of the literature search are described in Appendix A. The full-text assessment identified 11 eligible studies. These studies were subsequently assessed based on three criteria: The size of the sample, how well the patient population matched the potential Danish patient population and whether the aim of the study was to investigate adverse events associated with dialysis. Based on these criteria, we assessed that the recent meta-analysis published by Swai et al. (58,59) was the most suitable. The study separately reported the risk of all-cause infections and all-cause cardiovascular events for patients treated with haemodialysis and peritoneal dialysis.

Table 26 presents the follow-up times for each study included in the meta-analysis for all-cause cardiovascular events and for all-cause infections. From the study-specific follow-up times, we calculated the weighted average follow-up

times for each of the four endpoints, i.e., PD – all-cause cardiovascular events, HD – all-cause cardiovascular events, PD – all-cause infections, and HD – all-cause infections, as presented in the fourth column of Table 27. We used the weighted follow-up time in order to calculate the per-cycle risk of experiencing each adverse event, as presented in column five of Table 27.

Adverse reaction outcomes in the health economic analysis are summarised in Table 20. Table 26 shows the follow-up times from the studies included in the meta-analysis.

Table 26: Follow-up times from studies included in the meta-analysis.

	Follow up (years)		Weight from meta-analysis	
	HD	PD	All-cause cardiovascular events	All-cause infections
Chang 2012 (61)	N/A	N/A	19.1%	27.2%
Kang 2010 (62)	5.0	5.0	5.6%	24.6%
Kang 2011 (63)	5.0	5.0	5.6%	27.7%
Levy 2015 (64)	5.0	5.0	59.8%	-
Tsai 2019 (65)	6.3	6.0	6.5%	18.1%
Weng 2009 (66)	10.6	3.1	3.3%	2.5%

Table 27: Per-cycle risk of adverse events.

Adverse event		Aggregate risk	Weighted follow-up time	Risk per cycle (6 months)
All-cause cardiovascular events	PD	8.1%	5.0	0.81%
	HD	13.1%	5.3	1.22%
All-cause infections	PD	13.0%	5.2	1.26%
	HD	13.5%	5.5	1.23%

8.3 Extrapolation of relative efficacy

8.3.1 Time-to-event data – summarised

Allograft survival and survival with a functioning graft serve as key endpoints in the health economic analysis, as these determine model transitions between different health states. Allograft survival and survival with a functioning graft were estimated based on time-to-event data from all 46 patients who underwent a kidney transplant studied within the imlifidase clinical trials with a data cut-off in November 2021 (55).

No time-to-event data were available for patients receiving treatment with dialysis. As such, the survival probabilities for patients in dialysis treatment were extrapolated based on published relative survival ratios (the ratio of survival in patients in dialysis treatment to the survival expected given the age- and period-specific mortality of the general population).

8.3.2 Extrapolation of allograft survival

Death-censored graft survival using data from all 46 patients who underwent a kidney transplant studied within the imlifidase clinical trials showed that [redacted] of the patients had a functioning graft at six months. This rate remained at [redacted] by the end of the first and second years and decreased to [redacted] by the end of the third year (55).

These observed graft survival results were fitted with parametric functions (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma). Figure 9 presents the parametric models. Table 28 presents the parameters and goodness-of-fit criteria (as determined by AIC and BIC) for each of the models.

We apply the extrapolations based on time-to-event data from the total population of patients who have received treatment with imlifidase in the model base case, as this represents the most robust estimates of long-term allograft survival due to the limited number of patients included in the clinical trials.

[redacted]

Table 28: Parameters and goodness-of-fit criteria for graft survival, all imlifidase

Model	AIC	BIC	Parameter	Parameter value
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]

Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

All functions appear plausible at visual inspection, except for the Gompertz function, which seems to stagnate after approximately 10 years. Visual inspection suggests that the results produced by the generalised gamma and the exponential are the most conservative. Based on the AIC and BIC measures, the exponential function had the best statistical fit and was therefore selected as the most plausible curve to represent graft survival in the total population of patients treated with imlifidase. Moreover, the exponential function was the most conservative function with a converged variance-covariance.

8.3.3 Patient survival with a functioning graft

Data from all 46 patients who underwent a kidney transplant studied within the imlifidase clinical trials was used to estimate the survival with a functioning graft. Patients were censored when they lost their graft, and only survival with a functioning graft was considered in the predicted survival. An exponential function provided the best fit for the survival.

All patients receiving treatment with imlifidase were alive six months after transplant. At the end of the first year, [redacted] of patients were alive, and this proportion remained stable at the end of year two and three. This time-to-event data was fitted with standard parametric functions (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma). The estimated parametric distributions are presented in Figure 10. In addition, Table 29 presents the parameters and goodness-of-fit criteria (as determined by Akaike information criterion (AIC) and Bayesian information criterion (BIC)) for each of the models.

As was the case with allograft survival, we applied the extrapolations based on time-to-event data from the total population of patients who have received treatment with imlifidase in the model base case, as this represents the most robust estimates of long-term survival due to the limited number of patients included in the clinical trials.

Table 29: Parameters and goodness-of-fit criteria for patient survival with a functioning graft, all imlifidase

Model	AIC	BIC	Parameter	Parameter value
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]

All functions appear plausible at visual inspection, except for the Gompertz function, which seems to stagnate after approximately three years. Visual inspection suggests that the results produced by the exponential function were the most conservative. The exponential distribution was also considered the best fit based on the AIC and BIC criteria, as shown in Table 29. Thus, the exponential function was selected as the most plausible curve to represent survival with a functioning graft in the "all imlifidase" dataset.

8.3.4 Dialysis survival

Chaudhry et al. 2022 (3) investigated the survival benefit of transplantation versus dialysis in 34,467 patients from multiple countries in Europe who have undergone renal transplantation or who are on dialysis and are on a waiting list for a transplant. The meta-analysis provides a pooled hazard ratio (HR) for long-term, all-cause mortality at 0.49 for the transplantation group compared with the dialysis group in the European study population.

From Chaudhry et al. 2022 (3), we identified Sørensen et al. 2016 (41), who merged data from the Danish Nephrology Registry and Scandiatransplant between January 1995 and December 2011 to study the survival gains associated with kidney transplant. Controlling for cohort, age, sex, renal diagnosis and time on dialysis before entering, the study estimates a significant reduction in the risk of death for patients receiving kidney transplantation (HR=0.38). We apply this HR to study the impact on survival in the sensitivity analyses.

The HRs from these sources were applied to the OS curve for patients with a functioning graft in order to obtain the OS curve for patients on dialysis treatment.

Figure 11 shows the age-specific survival for kidney-transplanted patients and for patients in dialysis treatment applying the HR published in Chaudhry et al. 2022 and Sørensen et al. 2016.

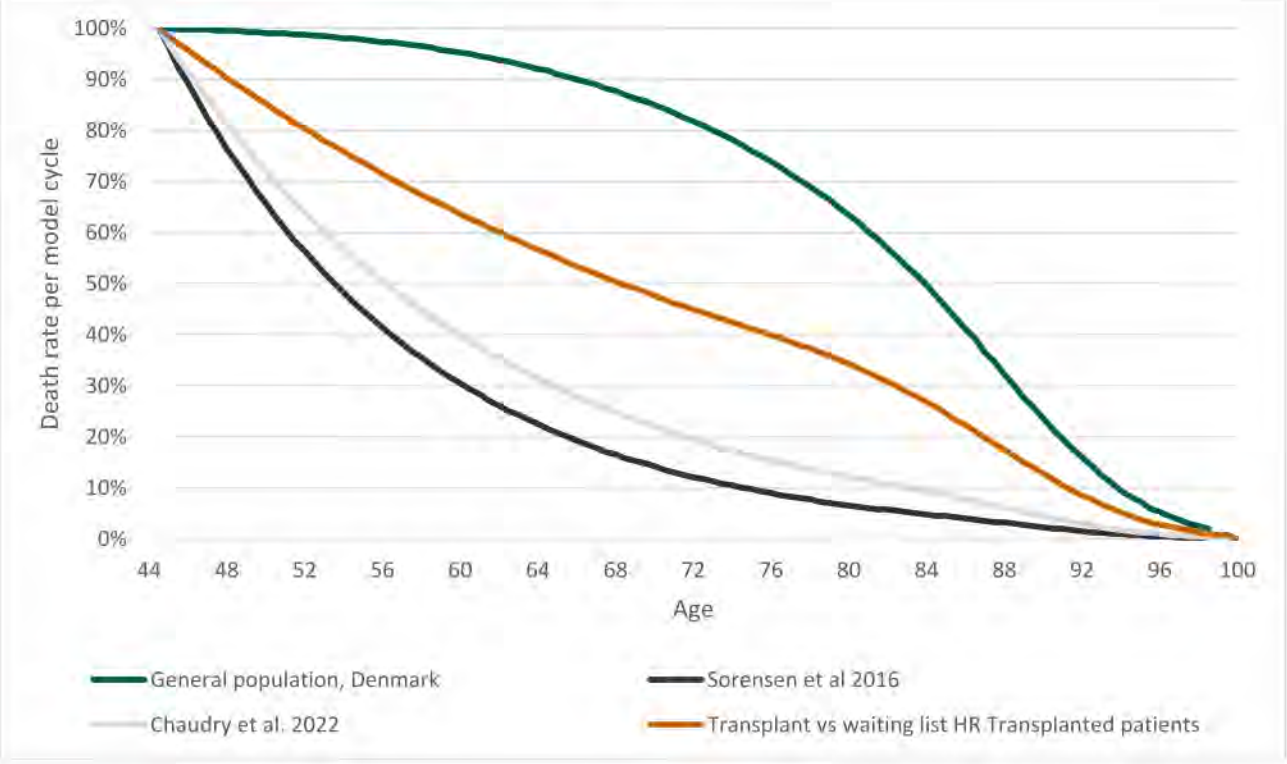

Figure 11: Comparison of survival for dialysis patients with kidney-transplanted patients and for the general population and dialysis patients in Denmark

8.3.5 Health state occupancy

Table 30 presents health state occupancy at relevant time points for patients receiving treatment with imlifidase and for patients in dialysis treatment.

Table 30: Health state occupancy for patients treated with imlifidase and patients in dialysis treatment

Year	Imlifidase			Dialysis (Chaudhry et al. 2022)		
	Dialysis	Functioning graft	Death	Dialysis	Functioning graft	Death
1	3.7%	93.4%	2.9%	92.3%	1.9%	5.8%
5	14.3%	71.2%	14.6%	71.6%	2.8%	25.5%
10	20.7%	50.6%	28.6%	53.5%	2.0%	44.5%
15	22.6%	36.0%	41.4%	40.0%	1.4	58.6%
25	19.9%	18.2%	61.9%	22.3%	0.7%	77.0%

8.4 Documentation of health-related quality of life (HRQoL)

HRQoL data were collected as part of the long-term study (Study 14), only post-transplantation. In Study 14, quality of life was assessed by means of general EQ-5D-5L questionnaires. No comparator arm was included in Study 14, and no HRQoL data for dialysis were available from Study 14. In addition, Study 14 was initiated after participants had been treated with imlifidase; therefore, no baseline utility values were available from the study. Due to the lack of high-quality HRQoL data for all the relevant health states, HSUV were identified from a systematic search of the literature.

8.4.1 Overview of health state utility values

We performed a systematic literature search to identify studies that included HRQoL data for kidney transplant and dialysis patients. A summary of the systematic literature review can be accessed in Appendix A. The systematic literature review included publications 2017 and up until July 2022 (date for performing the literature search). Through the systematic literature search, we finally identified two studies relevant for the purpose of documenting HSUV in the health economic model of imlifidase.

The two studies that were considered relevant for the health economic model were Lee et al 2005 (56) and Eriksson et al. 2017 (67). HSUV from the identified studies are presented in Table 31.

Table 31: Overview of HSUV derived from the literature search (presented in Appendix H)

	Results [SD]	Instrument	Comments
Dialysis			
Lee et al. 2005 (56) *Haemodialysis*	0.44 [0.32]	EQ-5D-3L	EQ-5D-3L data were collected in a cohort study including renal failure patients from the UK.
Lee et al. 2005 (56) *Peritoneal dialysis*	0.53 [0.34]	EQ-5D-3L	EQ-5D-3L data were collected in a cohort study including renal failure patients from the UK.
Eriksson et al. 2017(67) *Dialysis*	0.73 [0.22]	EQ-5D-3L	EQ-5D data were collected in a multi-site study including patients from the Nordic countries with autosomal dominant polycystic kidney disease.
Transplant patients			
Lee et al. 2005 (56)	0.71 [0.27]	EQ-5D-3L	EQ-5D-3L data were collected in a cohort study including renal failure patients from the UK.
Eriksson et al. 2017 (67)	0.85 [0.16]	EQ-5D-3L	EQ-5D data were collected in a multi-site study including patients from the Nordic countries with autosomal dominant polycystic kidney disease.
Study 14	0.8 SE 0.0	EQ-5D-5L	Three-year EQ-5D-5L data were collected for 13 patients. The data collected at this time should be interpreted with caution, since only few patients have had more than one visit.

HSUV from Lee et al. 2005 (56) were included in the base case to have HSUV associated with each of the three health states from the model (HD, PD, and functioning graft following transplant). While Eriksson et al. 2017 (67) provided HSUV based on patients from the Nordic countries using a DK tariff, the covered health states only included dialysis vs functioning graft following transplant. Additionally, the study population includes patients with autosomal dominant polycystic kidney disease (AKD). AKD is a genetic disease, and the patients in the study will likely differ from the normal imlifidase recipient, as AKD patients are often transplanted at an earlier disease stage, and thus will not have received dialysis for as great a period of time. Moreover, it should be noted that the HSUVs from Eriksson et al. 2017 (67) are higher than the values considered by the DMC for the general population. It seems unrealistic that chronic patients should have higher QoL than the general population, which points to bias in the estimates. Therefore, results from the sensitivity analyses including HSUV from Eriksson et al. 2017 (67) should be interpretated with caution.

8.4.2 Health state utility values used in the health economic model

Health state utility decrements in the model were calculated based on Lee et al. 2005 **(56)**. This was a UK cohort study identified through two publications we identified in the systematic literature search. The study summarised utility

data for HD, PD and renal transplant patients from a total of 416 patients. The study reported utilities derived from the five-dimension, three-level EuroQol questionnaire (EQ-5D-3L), which is the measure pertinent to the health economic model for imlifidase. Table 32 reports the mean utility from Lee et al. 2005 (56) for HD, PD and transplanted patients.

In the model, patients who receive a transplant after treatment with imlifidase are assumed to have a HSUV of 0.71Patients receiving dialysis are assumed to have a HSUV of 0.44 and 0.53 for HD and PD, respectively.

Utility decrements associated with adverse events were not applied in the model and therefore not identified through a systematic search of the literature. This was based on the assumption that the identified HSUV for each of the three health states already includes the utility decrement associated with the adverse events experienced by the average patient on dialysis or transplanted patient.

Table 32: Summary of the HSUV used in the model

Health state	HSUV	95% CI	Source
Transplanted patient with functioning graft	0.71	0.67-0.75	Lee et al. 2005 (56)
Haemodialysis	0.44	0.38-0.50	Lee et al. 2005 (56)
Peritoneal dialysis	0.53	0.45-0.61	Lee et al. 2005 (56)

Age adjustments

The HSUV has been adjusted for age according to the guideline from the DMC to account for the increased morbidity and mortality associated with increased age (57). Table 33 presents the population utilities applied as basis for the age adjustments and the adjustment index. The mean age in Lee et al. 2005 (56) was 58.7 years, 63.0 years and 52.8 years for PD, HD and transplanted patients, respectively. This corresponds to an age-adjustment of 0.981. Based on this, we calculated the HSUVs for functioning graft, haemodialysis, and peritoneal dialysis.

Table 33: Population utilities

Age group	Adjustment index	Functioning graft	Haemodialysis	Peritoneal dialysis	Dialysis weighted average
≤49	1.000	0.724	0.449	0.540	0.467
50-69	0.981	0.710	0.440	0.530	0.458
70-79	0.975	0.706	0.437	0.527	0.455
80+	0.865	0.626	0.388	0.467	0.404

Figure 12 illustrates the health state utilities from Lee et al. 2005 (56) after the age-dependent index adjustment and the health utilities by age derived from the general population (57).

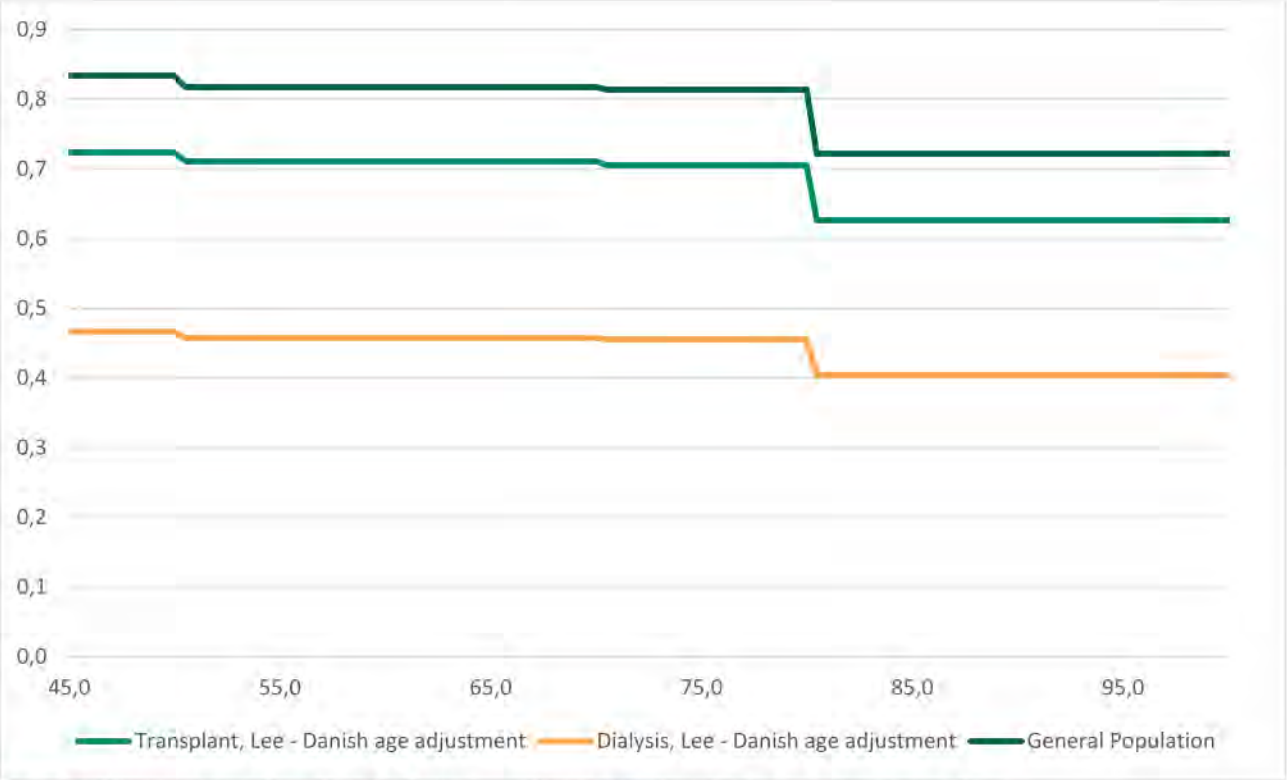

Figure 12: Utilities derived from Lee et al. 2005 – Danish adjustment index vs general population

8.5 Resource use and costs

In this section, we present the identified use of resources and the applied unit costs. Overall, the resource use and the estimated costs included in the analysis can be categorised as:

- Cost of imlifidase treatment
- Transplant procedure costs
- Cost of transplantation follow-up
- Cost of dialysis
- End-of-life costs
- Adverse event costs

8.5.1 Imlifidase treatment

The resource use and costs associated with imlifidase treatment are summarised in Table 34.

Imlifidase is provided as freeze-dried (lyophilised) powder which is reconstituted in sterile water to form concentrate. A calculated volume of the concentrate is added to a sodium chloride infusion solution for administration through IV under supervision. In the model, the imlifidase dosage is based on the proportion of patients [redacted] patients required at second dose of imlifidase to become crossmatch-negative (55). The pharmacy purchase price (PPP) of imlifidase was extracted on 10 May 2022 from Medicinpriser.dk (68) and was DKK 2,215,620 for one package

containing two vials of imlifidase. The model assumes that there are no additional costs associated with the administration or monitoring of imlifidase, as it is administered in the hours before a kidney transplant, while the patient is already in pre-surgery care.

According to the SPC for imlifidase, patients should receive premedication with corticosteroids and antihistamines to reduce the risk of infusion reactions (1). In Denmark, sensitised patients are already treated with these drugs during kidney transplantations (60); thus, these costs are not relevant for the imlifidase treatment. Instead, these costs are included in section 8.5.3.2 (immunosuppression drugs).

Patients treated with imlifidase should, in addition, receive standard of care induction T-cell-depleting agents with or without B-cell-depleting agents, i.e., imlifidase does not eliminate the need for standard of care immunosuppressive therapy (1). These costs are also included in section 8.5.3.2 (immunosuppression drugs).

According to the SPC for imlifidase, respiratory tract infections are the most common infections in patients with hypogammaglobulinemia (due to imlifidase), and prophylactic oral antibiotics covering respiratory tract pathogens should be added to the standard of care for four weeks (1). We consulted with a Danish clinical expert, who informed that phenoxymethylpenicillin 800 mg/day could be used as a prophylactic treatment against respiratory tract pathogens (60). We extracted the cost of phenoxymethylpenicillin 800 mg tablets on Medicinpriser.dk (68) on 4 May 2022. The PPP of 20 tablets was DKK 20, resulting in a total cost of DKK 28 for a 28-day period.

In total, we estimate that the average imlifidase drug cost per treatment is DKK 2,465,846.

Table 34: Estimated imlifidase drug cost per treatment

Parameter	Proportion of patients	Cost per treatment (DKK)	Source/comment
Imlifidase unit cost (2 vials)		2,215,620	Medicinpriser.dk (68), price extracted on 10 May 2022
Patients requiring 1 vial (≤44kg)	[redacted]	[redacted]	Proportion: data on file (55)
Patients requiring 2 vials (44–88kg)	[redacted]	[redacted]	Proportion: data on file (55)
Patients requiring 3 vials (≥88kg)	[redacted]	[redacted]	Proportion: data on file (55)
Average patient cost of imlifidase (first dose)		[redacted]	
Average patient cost of imlifidase including those requiring a second dose	[redacted]	[redacted]	Proportion: data on file (55)
Cost of co-medication (phenoxymethylpenicillin 800 mg/day)	100%	28	Medicinpriser.dk (68), price extracted on 4 May 2022
Total average patient cost of treatment with imlifidase		2,465,846	

8.5.2 Transplant procedure

The resource use and costs related to the transplant procedure are divided into three categories: direct costs, transportation costs and patient time cost.

8.5.2.1 Direct costs

The healthcare costs associated with renal transplantation are summarised in Table 35.

The healthcare costs associated with renal transplantation were calculated based on the weighted average of the DRG tariff for kidney transplantation (11MP02) and complicated kidney transplantation (11MP01). The weights used were provided by Jensen et al. 2014, who reported that 89% of kidney transplantations were non-complicated and 11% were complicated (69). We also included the cost of removing the old dialysis catheter. We used the DRG code 11MA98 (day surgery) to estimate the cost of removing the old dialysis catheter.
Based on the interview we had with the Danish clinical expert, we also included two DSA crossmatch tests, as we were informed that this was a realistic estimate of additional DSA crossmatch tests used when patients are treated with imlifidase. The cost of DSA crossmatch tests was based on the DRG code 36PR07.
In total, we estimate that the direct renal transplant cost per procedure is DKK 302,156.

It is assumed that all patients receiving imlifidase subsequently receive transplantation. This is based on the following: The overall efficacy dataset consists of 46 patients who received full dose of imlifidase and received transplantation. The safety dataset (54 patients in total) is a pooled analysis from the 46 transplanted patients + eight patients who were exposed to imlifidase but were not intended to receive transplants. All patients that were crossmatch-positive before treatment with imlifidase were converted to negative within 24 hours. PKPD (pharmacokinetic/pharmacodynamic) modelling showed that at two hours after administration of 0.25 mg/kg imlifidase, a crossmatch test is likely to become negative in 96% of the patients, and after six hours, at least 99.5% of the patients are likely to become crossmatch-test negative. The additional phase II trial 13-HMedIdeS-02 (n=8) was performed in sensitised CKD stage 5 patients, and transplantation was not an endpoint. Treatment protocols, tests and procedures (and a donor organ) that are included in transplantation were not in place, as this study was a dose-finding, PKPD, safety study. Hence, it is not the case that 15% did not reach the threshold value to be eligible for transplantation. One patient in trial 15-HMedIdeS-06 discontinued after a partial dosing of imlifidase due to an allergic reaction.
To address this, we have conducted a sensitivity analysis where we assume that 2.1% (1/47) of the imlifidase-treated patients in the clinical setting will not undergo transplantation (see section 8.7.2).

Table 35: Estimated renal transplantation cost per treatment

Parameter	Units/proportion	Cost per procedure (DKK)	Source/comment
Kidney transplantation	89%	262,079	Cost: DRG code 11MP02; proportion: Jensen et al. 2014 (69)
Kidney transplantation, complicated	11%	546,270	Cost: DRG code 11MP01; proportion: Jensen et al. 2014 (69)
Removal of dialysis catheter	1	2,038	Cost: DRG code 11MA98 (day surgery); units: Danish clinical expert (60)

Parameter	Units/proportion	Cost per procedure (DKK)	Source/comment
DSA crossmatch test	2	3,389	Cost: DRG code 36PR07 is assumed; units: Danish clinical expert (60)
Total cost per procedure		302,156	

8.5.2.2 Transportation costs

The cost of transportation in relation to the transplant procedure is based on the assumption that patients have one visit to the hospital. The cost per visit is based the DMC's guide to valuation of unit costs and is set to DKK 140 per visit (70). Thus, the transportation cost related to renal transplantation is estimated to be DKK 140 per procedure.

8.5.2.3 Patient time costs

The cost of patient time related to renal transplantation is primarily based on the average "trimpunkt" (the maximum length of stay included in the DRG tariff) for the DRG codes for kidney transplantation (11MP02) and complicated kidney transplantation (11MP01). As such, we assumed that patients are on average admitted to the hospital for 19 days in relation with a renal transplantation. The patient time spent is estimated as the expected length of admission in days multiplied by 24 hours. The cost of every hour spent is DKK 181 and is based on the DMC's guide to valuation of unit costs (70). In addition to the time spent admitted to the hospital, we also included the cost of time related to transportation. We assumed that a one-way visit to the hospital is associated with 30 minutes of travel, resulting in a total of one hour of transportation.

In total, we estimate that the cost of patient time associated with renal transplantation is DKK 82,717.

Table 36: Patient time cost related to renal transplantation

Parameter	Hours spent	Cost of patient time per procedure (DKK)	Source/comment
Cost of renal transplantation time	456	82,536	Hours spent: "Trimpunkt" for DRG codes 11MP01 and 11MP02; cost: the DMC's guide to valuation of unit costs (70)
Cost of transportation time	1	181	Hours spent: assumed; cost: the DMC's guide to valuation of unit costs (70)
Total	457	82,717	

8.5.3 Transplantation follow-up

The resource use and costs related to transplantation follow-up are divided into four categories: direct costs, Immunosuppression drugs, transportation costs and patient time cost.

8.5.3.1 Direct costs

The healthcare costs associated with follow-up for renal transplantation are summarised in Table 37.

The resource use associated with transplantation follow-up visits is based on the interview we had with the Danish clinical expert (60). We were informed that patients usually have 15-20 follow-up visits to the hospital in the first six months after transplantation. In the analysis, we assume that the average patient has 18 follow-up visits to the hospital in this period. In the following 7-12 months, patients have on average six follow-up visits, while patients have on average four follow-up visits the following years (60). We were also informed that patients, in addition the regular follow-up visits, were offered an annual DEXA scan (bone density scan) due to the steroid medication they receive.

The cost of follow-up visits at the hospital was based on DRG code 23MA04, while the cost of a DEXA scan is based on the DRG code 36PR08. As the DEXA scan is only required once yearly, the cost of this is not counted during the first two model cycles.

Furthermore, we were informed by the Danish clinical expert that management of kidney-transplanted patients is exclusively or almost exclusively done by the hospitals. In some cases, patients who live far from the hospital will occasionally give blood samples at their general practitioner instead of going to the hospital for follow-up visits, but this is rare. For this reason, we assumed that management of follow-up visits related to renal transplantation was completely accrued by the Danish regions.

Table 37: Estimated follow-up costs related to renal transplantation

Parameter	Units/visits	Cost per procedure/cycle (DKK)	Source/comment
Cost per follow-up visit	1	1,515	Cost: DRG code 23MA04 (control visit at the hospital)
Cost of annual DEXA scan	1	2,878	Cost: DRG code 36PR08; usage: Danish clinical expert (60)
Cost of follow-up visits (0-6 months)	18	27,270	Cost: DRG code 23MA04; number of visits: Danish clinical expert (60)
Cost of follow-up visits (7-12 months)	6	9,090	Cost: DRG code 23MA04; number of visits: Danish clinical expert (60)
Cost of follow-up visits incl. annual DEXA scan (Subsequent years)	4	8,938	Cost: DRG code 23MA04; number of visits: Danish clinical expert (60)

8.5.3.2 Immunosuppressive drugs

The unit costs of immunosuppressive drugs associated with renal transplantation are summarised in Table 38, and the dosages of immunosuppressive drugs and the resulting costs are summarised in Table 39.

This section includes both the cost of immunosuppressive drugs that are used in induction therapy (drugs used in relation to the transplation procedure) and maintenance therapy (drugs used to avoid rejection and the loss of the renal allograft after the transplantation).

There is currently no specific treatment protocol in Denmark for transplantations with imlifidase. Instead, we consulted a Danish clinical expert regarding the drug treatment regime associated with renal transplantation on sensitised patients (60). We were informed that the drug recommendation from the DMC for immunosuppressants associated with kidney transplantation (36) was not applicable for sensitised patients.
The Danish clinical expert informed us that the induction therapy constituted the use of Thymoglobolin® (anti-thymocyte globulin) with a dosage of 1 mg/kg. Usually, a total of five dosages would be given in two-day intervals. We calculated the total dosage of Thymoglobolin® by multiplying the number of dosages with the dosage per kilo and average patient weight in the imlifidase trials (72.2kg) (55). In addition to Thymoglobolin®, we were informed that the induction therapy included the use of steroids (prednisolone 160 mg) and antihistamine (Clemastin 2 mg) to avoid infusion reactions related to the Thymoglobolin® treatment.

We were informed that the maintenance therapy for sensitised patients usually consisted of Adport 0.15 mg/kg daily and Myfenax 2,000 mg daily. The total dosage of Adport was calculated using the average patient weight in the imlifidase trials (72.2kg) (55). We were further informed that patients would receive 40 mg of prednisolone the first week after transplantation. After the first week, the dosage would be reduced to 20 mg and gradually reduced further until a dosage of 7.5 mg is reached three months after transplantation. The dosage is then further reduced to 5 mg six months after transplantation. The 5 mg dosage is continued permanently until loss of the renal allograft (60).

The unit costs of the immunosuppressive drugs are presented in Table 38 and the dosage of immunosuppressive drugs used per cycle and the resulting costs are shown in Table 39.

Table 38: Unit costs of immunosuppressive drugs related to renal transplantation

Parameter	Cost per pack, PPP (DKK)	Pack size (mg)	Cost per mg, PPP (DKK)	Source/comment
Thymoglobolin®	1,203	25	48	Medicinpriser.dk, extracted on 4 May 2022 (68)
Myfenax (mycophenolate mofetil)	489	50,000	0.01	Medicinpriser.dk, extracted on 4 May 2022 (68)
Adport (tacrolimus)	2,894	250	12	Medicinpriser.dk, extracted on 4 May 2022 (68)
Steroids (prednisolon)	38	500	0.08	Medicinpriser.dk, extracted on 4 May 2022 (68)
Clemastin (antihistamine)	471	10	47	Medicinpriser.dk, extracted on 4 May 2022 (68)

Table 39: Dosages of immunosuppressive drugs related to renal transplantation and the resulting costs

	Dose (mg)			Costs (DKK)		
Parameter	Dose, cycle 1	Dose, cycle 2	Dose, cycle 3+	Cost, cycle 1	Cost, cycle 2	Cost, cycle 3+
Thymoglobolin®	361	-	-	17,365	-	-
Myfenax (mycophenolate mofetil)	366,000	364,000	365,000	3,582	3,562	3,572
Adport (tacrolimus)	1,982	1,971	1,976	22,944	22,819	22,882
Steroids (prednisolone)	2,375	910	913	182	70	70
Clemastin (antihistamine)	2	-	-	94	-	-
Total cost	-	-	-	44,168	26,451	26,524

8.5.3.3 Transportation costs

The cost of transportation associated with renal transplant follow-up visits is based on the number of times patients go the follow-up visits per cycle (section 8.5.2.1). The cost per visit is based on the DMC's guide to valuation of unit costs and is set to DKK 140 per visit (70). The cost per cycle was calculated by multiplying the number of follow-up visits by the cost of transportation per visit. Table 40 shows the transportation costs associated with follow-up visits.

Table 40: Transport costs associated with renal transplant follow-up visits

Parameter	Number of visits	Cost of transportation per cycle (DKK)	Source/comment
Transportation (0-6 months)	18	2,520	Cost: DMC valuation of unit costs (70); number of visits: Danish clinical expert (60)
Transportation (7-12 months)	6	840	Cost: DMC valuation of unit costs (70); number of visits: Danish clinical expert (60)
Transportation (subsequent years)	4	Annual cost: 560; cycle cost: 280	Cost: DMC valuation of unit costs (70); number of visits: Danish clinical expert (60)

8.5.3.4 Patient time costs

The cost of patient time related to renal transplantation is based on the time patients spend at the follow-up visits at hospital and the time they spend on transportation to the follow-up visits (Table 41). The cost of every hour spent is set to DKK 181 and is based on the DMC's guide to valuation of unit costs (70).

The time spent per follow-up visit is based on information provided by a Danish clinical expert who informed that a follow-up consultation usually lasts 30 minutes. The total time spent at follow-up visits is calculated by multiplying the length of a consultation with the number of consultations per cycle. The number of follow-up visits is described in

section 8.5.3.1. It is assumed that there is no additional time associated with the DEXA scan, as the scan is performed during a follow-up visit (60).

The cost of time spent on transportation is calculated based on the number of follow-up visits in each cycle and the time spent on transportation for each visit. We assumed that a one-way visit to the hospital is associated with 30 minutes of travel, resulting in a total of one hour of transportation per visit.

Table 41: Patient time cost related to follow-up visits

Parameter	Number of visits	Hours per visit	Cost of patient time per cycle (DKK)	Source/comment
Cost of follow-up time (0-6 months)	18	0.5	1,629	Hours spent per visit: Danish clinical expert (60); cost: the DMC's guide to valuation of unit costs (70)
Cost of follow-up time (7-12 months)	6	0.5	543	Hours spent per visit: Danish clinical expert (60); cost: the DMC's guide to valuation of unit costs (70)
Cost of follow-up time (subsequent years)	4	0.5	Annual cost: 362; cycle cost: 181	Hours spent per visit: Danish clinical expert (60); cost: the DMC's guide to valuation of unit costs (70)
Cost of transportation time (0-6 months)	18	1	3,258	Hours spent per visit on transportation: assumed; cost: the DMC's guide to valuation of unit costs (70)
Cost of transportation time (7-12 months)	6	1	1,086	Hours spent per visit on transportation: assumed; cost: the DMC's guide to valuation of unit costs (70)
Cost of transportation time (subsequent years)	4	1	Annual cost: 724; cycle cost: 362	Hours spent per visit on transportation: assumed; cost: the DMC's guide to valuation of unit costs (70)

8.5.4 Dialysis

The resource use and costs related to dialysis are divided into three categories: direct costs, transportation costs and patient time cost.

8.5.4.1 Direct costs

The healthcare costs associated with dialysis are calculated for both in-centre haemodialysis (dialysis at the hospital), home haemodialysis (haemodialysis in the patients' own home) and peritoneal dialysis (also in the patients' own home).

The cost of in-centre haemodialysis is based on the DRG code 11PR10, which denotes the cost per dialysis session. The annual number of in-centre haemodialysis session was set to 156 and was based on input from the Danish clinical

expert (60). We were informed by the Danish clinical expert that patients in in-centre haemodialysis are rarely going to control visits as they are already treated at the hospitals three times per week. We were, however, informed that control consultations were usually held once every six months. The cost of these control consultations is based on the DRG code 23MA04. Table 42 summarises the cost of in-centre haemodialysis.

Table 42: Estimated costs related to in-centre haemodialysis

Parameter	Units	Cost per unit (DKK)	Cost per year (DKK)	Source/comment
In-centre haemodialysis	156	3,074	479,544	Units: Danish clinical expert (60); cost: DRG code 11PR10
Control consultations	2	1,515	3,030	Units: Danish clinical expert (60); cost: DRG code 23MA04
Total cost per year			482,574	

The cost of home haemodialysis is based on the DRG code 11PR06. The cost of DRG code 11RP06 does not represent the cost per dialysis session, but rather the total cost of dialysis between control visits at the hospital. We were informed by the Danish clinical expert that patients usually go to follow-up visits once every six weeks, meaning that patients on average have 8.7 control visits each year (60). Table 43 summarises the cost of home haemodialysis.

Table 43: Estimated costs related to home haemodialysis

Parameter	Units	Cost per unit (DKK)	Cost per year (DKK)	Source
Home haemodialysis control	8.7	18,180	157,566	Units: Danish clinical expert (60); cost: DRG code 11PR06

The cost of peritoneal dialysis is based on DRG code 11PR07. As with the DRG code for home haemodialysis, this DRG code does not represent the cost per dialysis session, but rather the total cost of dialysis between control visits at the hospital. We were informed by the Danish clinical expert that patients usually go to follow-up visits once every six weeks, meaning that patients on average have 8.7 control visits each year (60). In addition to the dialysis costs, patients on peritoneal dialysis sometimes require home assistance to manage their dialysis, as it is performed in their own home. We estimate that 8.9% of patients on peritoneal dialysis require home assistance, as this was stated in a report from the Danish Health Authority (71). The cost of home assistance per dialysis session was also estimated in the report from the Danish Health Authority and was set to DKK 425 per session. We were informed by the Danish clinical expert that patients on peritoneal dialysis require dialysis almost daily. In the model, we assumed that the annual number of dialysis sessions was 364 (60). Table 44 summarises the cost of peritoneal dialysis.

Table 44: Estimated costs related to peritoneal dialysis

Parameter	Units (proportion of patients)	Cost per unit (DKK)	Cost per year (DKK)	Source
Peritoneal dialysis control	8.7	15,879	137,623	Units: Danish clinical expert (60); cost: DRG code 11PR07
Home assistance	364 (8,9%)	425	13,762	Units: Danish clinical expert (60); proportion: the Danish Health Authority (71); cost: the Danish Health Authority (71)
Total cost per year			151,385	

We were informed by the Danish clinical expert that management of dialysis patients is exclusively managed by the hospitals, except for home assistance in relation to peritoneal dialysis, which is managed by the municipalities. As such, it may seem that the municipalities have expenses related to their services; however, agreements between the municipalities and the Danish regions denote that the municipalities are reimbursed by the regions in relation to the home assistance, and thus, all costs related to dialysis are accrued by the regions (72–74).

The average weighted cost per dialysis patient per year was calculated using data from the Danish Nephrology Registry, Annual Report 2020 (75), which reported the amount of patients using in-centre dialysis, home haemodialysis and peritoneal dialysis (Table 45). Out of the 2,537 patients in Denmark who are on dialysis, 14 patients are included in irregular dialysis programmes (hybrid dialysis and in-centre peritoneal dialysis). In the model, we did not include these patients, as it was considered a negligible amount. The distribution between in-centre dialysis, home haemodialysis and peritoneal dialysis that is used in the model is shown in Table 45. We consulted the Danish clinical expert regarding the dialysis distribution for sensitised patients. We were informed that sensitised patients have the same dialysis treatment distribution as the full dialysis population reported in the Danish Nephrology Registry, Annual Report 2020 (both before transplantation and after graft loss) (60).

Table 45: Estimated cost per dialysis session

Parameter	Proportion	Cost per year (DKK)	Cost per cycle (DKK)	Source/comment
In-centre haemodialysis	73.8%	482,574	241,287	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: Table 42
Home haemodialysis	6.6%	157,566	78,783	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: Table 43
Peritoneal dialysis	19.6%	151,385	75,693	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: Table 44
Weighted average per dialysis patient		396,084	198,042	

Training in home dialysis is a requirement before patients can start using home haemodialysis or peritoneal dialysis. The cost of training was also included in the model and is based on the DRG code 11PR08, which denotes the cost of

training related to home peritoneal dialysis. As there are no DRG code for training related to home haemodialysis, we assumed that the cost of training related to this is equal to the cost of home peritoneal dialysis. The cost of training was included in the model by multiplying the DRG tariff (11PR08) by the amount of patients on home haemodialysis and peritoneal dialysis (26,2%), and by the amount of new patients who lose their graft every cycle. The cost of home dialysis training is summarised in Table 46.

Table 46: Estimated costs related to home dialysis training

Parameter	Proportion	Cost of training per patient in home dialysis (DKK)	Weighted cost per dialysis patient (DKK)	Source/comment
Cost of training	26.2%	18,381	4,823	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: DRG code 11PR08

8.5.4.2 Transportation costs

The cost of transportation associated with dialysis treatment is based on the number of times patients go to the hospital per year in relation to dialysis and the proportion of patients receiving each type of dialysis (see section 8.5.4.1). The transportation cost per visit is based on the DMC's guide to valuation of unit costs and is set to DKK 140 per visit (70). The cost per year was calculated by multiplying the annual number of visits to the hospital by the proportion of patients receiving each type of dialysis by the cost per visit. Table 47 shows the transportation costs associated with dialysis treatment.

Table 47: Transport costs associated with dialysis treatment

Parameter	Proportion	Visits per year	Cost per year (DKK)	Cost per cycle (DKK)	Source/comment
In-centre haemodialysis	73.8%	156	21,840	10,920	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60)
Home haemodialysis	6.6%	8.7	1,213	607	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60)
Peritoneal dialysis	19.6%	8.7	1,213	607	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60)
Weighted average per dialysis patient			16,428	8,214	

The cost of transportation associated with home dialysis training is also included in the model. The number of visits related to dialysis training is based on information from rigshospitalet.dk, where its reported that peritoneal dialysis training usually takes 4-10 sessions at the hospital (76). The number of visits related to home haemodialysis training is individual but is usually completed over a course of three months. In the model, we assume that the number of visits related to home haemodialysis training is equal to the number for peritoneal dialysis (77). Furthermore, in the analysis we assumed that the average number of training sessions is seven. The transportation costs related to training were calculated by multiplying the number of visits to the hospital by the proportion of patients in home dialysis by the cost per visit (DKK 140). The cost of transportation related to training is only included for new patients who lose their graft every cycle. The costs of transportation related to home dialysis training are summarised in Table 48.

Table 48: Transport costs associated with home dialysis training

Parameter	Proportion	Visits	Cost of transport related to training per dialysis patient (DKK)	Source/comment
Home haemodialysis	6.6%	7	980	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: assumed
Peritoneal dialysis	19.6%	7	980	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: rigshospitalet.dk (76)
Weighted average per dialysis patient			257	

8.5.4.3 Patient time costs

The cost of patient time related to dialysis treatment is based on the time patients spent on dialysis treatment, time spent on control visits, time spent on transportation and time spent on home dialysis training. The cost of every hour spent is DKK 181 and is based on the DMC's guide to valuation of unit costs (70). The proportion of patients in in-centre dialysis, home haemodialysis and peritoneal dialysis was used to calculate a weighted average for a dialysis patient.

The time spent on in-centre haemodialysis per session is usually four hours (78), while the time spent per home haemodialysis session is about three hours (79). The time spent on peritoneal dialysis depends on which subtype (automated peritoneal dialysis (APD) or continuous ambulatory peritoneal dialysis (CAPD)) patients are using. Patients using APD are using a machine that automatically changes the dialysis fluid at night. It takes approximately 15 minutes every night to prepare the machine. As patients are sleeping while the dialysis is performed, we have only included the 15 minutes it takes to prepare the APD (80). Patients using CAPD must manually change the dialysis fluid four times per day. It takes approximately 30 minutes to change the fluid, meaning patients spend about two hours every day on dialysis (78). The number of treatments required for each type of dialysis is based on inputs from a Danish clinical expert (60): in-centre haemodialysis patients require 156 treatments, home haemodialysis patients require 208, and peritoneal dialysis (both APD and CAPD) patients require 364 treatments. The patient time cost related to dialysis treatment is summarised in Table 49.

Table 49: Patient time cost related to dialysis treatment

Parameter	Proportion of patients	Hours per treatment	Treatments per year	Cost per year (DKK)	Cost per cycle (DKK)	Source/comment
In-centre haemodialysis	73.8%	4	156	112,944	56,472	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours per treatment: sundhed.dk (78)
Home haemodialysis	6.6%	3	208	112,944	56,472	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours per treatment: nyre.dk (79)
Peritoneal dialysis	19.6%					Proportion: Danish Nephrology Registry, Annual Report 2020 (75)
APD	44% of patients in peritoneal dialysis	0.25	364	16,471	8,236	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours per treatment: nordsjaellandshospital.dk (80)
CAPD	56% of patients in peritoneal dialysis	2	364	131,768	65,884	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours per treatment: sundhed.dk (78)
Weighted average per dialysis patient				106,675	53,337	

The time spent per control visit is based on information provided by a Danish clinical expert, who informed that a control consultation usually lasts 30 minutes for in-centre haemodialysis patients and 20 minutes for home dialysis patients. The total time spent at follow-up visits is calculated by multiplying the length of a consultation by the number of consultations per cycle. The number of follow-up visits is described in section 8.5.4.1. Table 50 summarises the patient time cost related to control visits at the hospital.

Table 50: Patient time cost related to control visits at the hospital

Parameter	Proportion of patients	Hours per visit	Visits per year	Cost per year (DKK)	Cost per cycle (DKK)	Source/comment
In-centre haemodialysis	73.8%	0.5	2	181	91	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours per visit: Danish clinical expert (60)
Home haemodialysis	6.6%	0.33	8.7	522	261	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours per visit: Danish clinical expert (60)
Peritoneal dialysis	19.6%	0.33	8.7	522	261	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours per visit: Danish clinical expert (60)
Weighted average per dialysis patient				271	135	

The time spent on transportation is based on the number of times patients go to the hospital. Patients in in-centre haemodialysis go to the hospital 156 times per year, as this is the number of treatments per year. There is no transportation included for control visits for in-centre haemodialysis patients, because we were informed that these controls were conducted in extension of a regular dialysis session. Patients on home haemodialysis and peritoneal dialysis go to the hospital 8.7 times per year, as this is the required number of controls for these patients.

The cost of time spent on transportation is calculated based on the number of visits per year and the time spent on transportation for each visit. We assumed that a one-way visit to the hospital is associated with 30 minutes of travel, resulting in a total of one hour of transportation per visit. Table 51 summarises the patient time cost related to transportation for dialysis patients.

Table 51: Patient time cost related to transportation for patients on dialysis treatment

Parameter	Proportion of patients	Number of visits per year	Cost of patient time per year (DKK)	Cost of patient time per cycle (DKK)	Source/comment
In-centre haemodialysis	73.8%	156	28,236	14,118	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours of transport per visit: assumed
Home haemodialysis	6.6%	8.7	1,569	784	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours of transport per visit: assumed
Peritoneal dialysis	19.6%	8.7	1,569	784	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); number of visits: Danish clinical expert (60); hours of transport per visit: assumed
Weighted average per dialysis patient			21,239	10,619	

The cost of patient time associated with home dialysis training is also included in the model. The cost of patient time is estimated based on the number of required training sessions and the hours spent per training session. The required number of training sessions is described in section 8.5.4.2. The time spent per session is based on rigshospitalet.dk, which informed that a peritoneal dialysis training session usually lasts 5.5 hours (76). We assumed that the time spent per session on home haemodialysis training is the same as the time spent on peritoneal dialysis training. Table 51 summarises the patient time cost related to home dialysis training.

Table 52: Patient time cost related to home dialysis training

Parameter	Proportion of patients	Hours per session	Number of sessions	Cost related to training per dialysis patient (DKK)	Source/comment
Home haemodialysis	6.6%	5.5	7	6,969	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); hours per session and number of sessions: assumed
Peritoneal dialysis	19.6%	5.5	7	6,969	Proportion: Danish Nephrology Registry, Annual Report 2020 (75); cost: the DMC's valuation of unit costs (70); hours

Parameter	Proportion of patients	Hours per session	Number of sessions	Cost related to training per dialysis patient (DKK)	Source/comment
					per session and number of sessions: rigshospitalet.dk (76)
Weighted average per dialysis patient				1,828	

8.5.5 End-of-life costs

In the model, end-of-life costs in terms of palliative care (e.g., at a hospice) are not included. Instead, it is assumed that patients are admitted to the hospital due to unspecified kidney-related diseases for 30 days before they die. In the model, we used the DRG code 11MA02 (other primary or secondary medical kidney disease without dialysis) to estimate the end-of-life costs. The "trimpunkt" for this DRG code is 11 days, meaning that the remaining 19 days of admission are based on the "langliggertakst", which is DKK 2,185 per additional day of admission (81). The end-of-life costs are assigned to all patients who die, regardless of whether they are transplanted or on dialysis. Table 53 summarises the end-of-life costs.

Table 53: End-of-life costs

Parameter	Units	Cost per unit (DKK)	End-of-life costs (DKK)	Source/comment
Other primary or secondary medical kidney disease without dialysis	1	33,289	33,289	Cost: DRG code 11MA02 assumed
"Langliggertakst"	19	2,185	41,515	Cost: the Danish Health Data Authority (81)
Total		257	74,804	

8.5.6 Adverse events

The adverse events included in the model are categorised into imlifidase-related AEs, transplant-related AEs and dialysis-related AEs. Transportation and patient time costs were not included for AEs.

8.5.6.1 Imlifidase-related adverse events

The model parameters relating to imlifidase treatment are summarised in Table 54, and note that transplant rejections are summarised in section 8.5.6.2 to avoid double-counting. The imlifidase AEs were only included in the first cycle, as patients are only treated once with the drug.

The risk of imlifidase-related AEs is based on the EPAR for imlifidase (2). The costs of the imlifidase-related AEs were based on DRG codes. The two AEs "infusion-related reaction" and "myalgia" were set to DKK 0, as patients in Denmark

are already treated with Clemastin (see section 8.5.3.2) to avoid infusion-related reactions during the transplantation. Furthermore, it is assumed that muscle relaxants are used in the treatment of myalgia. Baclofen, a muscle relaxant, costs DKK 14 (PPP) for 56 tablets (source: medicinpriser.dk, accessed on 9 April 2022 (68)). Thus, this cost is assumed to be negligible.

Table 54: Cost of imlifidase-related AEs

Imlifidase-related AEs (Cycle 1)	Risk (%)	Cost of AE (DKK)	Source/comment
Pneumonia	5.6	35,491	Risk: EPAR for imlifidase (2); cost: average DRG code for pneumonia and pleurisy, patients > 60 years old (04MA13) and 0-59 years old (04MA14) assumed
Sepsis	3.7	45,361	Risk: EPAR for imlifidase (2); cost: DRG code 18MA01 (sepsis)
Abdominal infection	1.9	35,699	Risk: EPAR for imlifidase (2); cost: DRG code 18MA03 for "postoperative and post-traumatic infections without complications" assumed
Catheter site infection	1.9	31,420	Risk: EPAR for imlifidase (2); cost: DRG code 09MA04 for "skin and subcutaneous tissue infections (patients >18 years old)" assumed
Parvovirus infection	1.9	40,002	Risk: EPAR for imlifidase (2); cost: DRG code 18MA08 for "other infections or parasitic diseases" assumed
Upper respiratory tract infection	1.9	52,911	Risk: EPAR for imlifidase (2); cost: Average DRG code for infections and inflammation of the respiratory tract, patients > 65 years old (04MA05) and 0-64 years old (04MA06) assumed.
Infusion-related reaction	1.9	-	Risk: EPAR for imlifidase (2); cost: assumed negligible
Myalgia	1.9	-	Risk: EPAR for imlifidase (2); cost: assumed negligible

8.5.6.2 Transplant-related adverse events

The transplant-related AEs included in the model are AMR, delayed graft function and complications related to graft loss.

The risk of AMR was based on study 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS- 04 and 15-HMedIdeS-06 (55). In these studies, no AMR events were reported after the first year. These data were used to inform the model probability of AMR in the first and second cycle of the model. The cost related to the treatment of AMR were based on the drugs and procedures used in the imlifidase studies. These treatments are presented in Table 55. The cost of each drug was calculated based on the proportion of patients receiving each drug, the average number of administrations, the average dose that patients received per administration, and the PPP, see Table 55 and Table 56. The procedure costs (plasmapheresis, splenic embolisation and splenectomy) were based on 2022 DRG tariffs. In addition, hospitalisation costs were estimated as eight days multiplied by the 'langliggertakst' (long-term hospitalisation tariff) from the 2022 DRG catalogue of DKK 2,185. The eight days were included based on the assumption that patients experiencing AMR had an average of eight hospitalisation days. This was assumed because the 'trimpunkt' for the DRG tariff '11MA03' is 12 days, and we find it plausible that eight days will be above the upper quartile (Q3) of the hospitalisation durations. The cost of an AMR is presented in Table 58.

Table 55: AMR treatments used in imlifidase studies and proportion receiving each treatment. Source: data on file.

AMR Treatments	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 56: Information on the drugs used for AMR treatment in the model. Source: medicinpriser.dk (November 2022).

Treatment	Active ingredient	Drug	Strength, mg	Package	PPP (DKK)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 57: Procedures used to treat AMR. Source: data on file.

Procedures	DRG-tariff	Description	Price (DKK)
[redacted]			

Table 58: Cost of antibody-mediated rejection

Transplant AEs	Risk cycle 1 (%)	Risk cycle 2 (%)	Cost (DKK)	Source/comment
AMR (Cycle 1)	[redacted]			Risks: Data on file (55)

Delayed graft function sometimes occurs after renal transplantations. The risk of delayed graft function was based on the imlifidase trials and was [redacted] (55). The resource use related to delayed graft function was based on input from a Danish clinical expert (60). We were informed that 14 days was a realistic duration of delayed graft function until the kidney gained its function. In the period until the graft gained function patients would remain in dialysis. In addition to this, patients would usually require two ultrasound scans of the kidney and one biopsy. The daily cost of dialysis was calculated by dividing the annual cost of dialysis (Table 45) by 365.25 days. The cost of ultrasound scans was based on the DRG code 09PR05, and the cost of a biopsy was based on the DRG code 30PR10. Table 59 summarises the cost of delayed graft function.

Table 59: Cost of delayed graft function

Parameter	Units	Cost per unit (DKK)	Cost per episode (DKK)	Source/comment
Dialysis	14	1,084	15,182	Risks: data on file (55); cost: see section 8.5.4.1
Ultrasound scan	2	1,883	3,766	Risks: data on file (55); cost: DRG code 09PR05
Biopsy	1	4,974	4,974	Risks: data on file (55); cost: DRG code 30PR10
Total cost of delayed graft function			23,922	

It should be noted that patients with delayed graft function had an average of [redacted] days delayed graft function, but overtime they reached the same eGFR as study patients without delayed function (see Figure 13). In the Swedish

cohort study (38) there was not one single case of delayed graft function. These events occurred in the US studies where the kidney travels long distances and cold ischemic time (CIT) thereby is prolonged. In US, machine perfusion was not used during the transport, however in Sweden it was. From Danish clinicians we understand that all clinics use Lifeport machine perfusion during the kidney transport in Denmark. This has demonstrated a significant improvement in avoiding delayed kidney function. Hence the conditions between Sweden and Denmark should be similar, with the difference that travel distances are even shorter in Denmark. Thus, we find it is reasonable to assume that kidney outcomes and patient survival could be superior in Denmark compared to the overall outcomes and survival for the full imlifidase study cohort. In Figure 14, we present a Kaplan Meier curve illustrating the time from transplantation to functioning graft.

A patient who loses their graft returns to dialysis; however, there are additional costs associated with a graft loss. Nephrectomy may be performed in case of a graft loss, and the patients who experience early graft failure are more likely to have their graft removed. The proportion of grafts explanted has previously been described in a NICE appraisal (82) (Table 60). We conferred these risks with a Danish clinical expert, who informed that the risk of nephrectomy in Denmark from month 0-3 was approximately 70% instead of 41%. The remaining risks were good approximations of Danish clinical practice.

Table 60: Risk of nephrectomy: Source: Jones-Hughes et al. 2016 (82) and Danish clinical expert (60).

Time since transplantation	Risk of nephrectomy
0-3 months	70%
3-12 months	23%
12-24 months	9%
More than 24 months	4%

As the model for imlifidase uses a six-month cycle length, an average of the 0 to 3 months and the 3 to <12 months was used for the proportion of nephrectomy in the first cycle (47%), 23% was used for the second cycle, 9% for the third and fourth cycles, and 4% on the remaining cycles of the model. We also consulted the Danish clinical expert on additional resource use related to graft loss. In addition to the cost of nephrectomy, we were informed that if the graft loss occurs within the first six months after transplantation, immunosuppressive therapy would be stopped, while steroids are maintained for three months. If the graft is lost after six months, immunosuppressive therapy would continue for an additional month, while steroids are maintained for three months.
Furthermore, in about 10% of the cases with graft loss, patients will require an insertion of a temporary tunnelled CVC and a re-access surgery to the transplanted kidney (60).

Table 61: Cost of graft loss

Parameter	% Utilisation	Cost of graft loss (DKK)	Source/comment
Nephrectomy (cycle 1)	47%	88,599	% utilisation: NICE appraisal (82) and Danish clinical expert (60); cost: average DRG code for "surgery on kidney, renal pelvis and ureter, malignant disease, PT >18 years" with robot surgery (11MP07) and without robot surgery (11MP08) assumed
Nephrectomy (cycle 2)	23%		
Nephrectomy (cycle 3)	9%		
Nephrectomy (cycle 4)	9%		
Nephrectomy (cycle 5)	4%		
Maintained immunosuppressant (Cycle 1)	100%	91	% utilisation: Danish clinical expert (60); cost: see section 8.5.3.2
Maintained immunosuppressant (Cycle 2)	100%	4,369	% utilisation: Danish clinical expert (60); cost: see section 8.5.3.2
Insertion of a temporary tunnelled CVC	10%	7,181	% utilisation: Danish clinical expert (60); cost: DRG code 11MP27 (surgery on vascular or lymphatic system)
Access surgery	10%	70,118	% utilisation: Danish clinical expert (60); cost: DRG code 11MP27 (other kidney and urinary tract surgeries)

8.5.6.3 Dialysis-related adverse events

All risks of dialysis-related AEs were based on a recent meta-analysis from Swai et al. (59). The risk calculations are described in section 8.2.2.5. The costs of the AEs were based on DRG tariffs. A summary of the resource use and costs related to peritonitis is shown in Table 62.

The ESRD population is subject to many complications, irrespective of the type of renal replacement therapy, beyond cardiovascular events and infections. Other AEs were not included in the economic model, as published detailed evidence relevant to the model was not identified. The absence of these AEs results in an underestimation of the costs associated with treatment with dialysis. This is supported by a UK study by Li et al. (2015) (83) that explored the aggregated all-cause inpatient and outpatient costs for patients on dialysis and for patients with a kidney transplant, excluding the cost of the transplant and the cost of dialysis itself. This study showed that the total cost differential for a patient continuing dialysis rather than receiving a transplant is considerable following the first year of renal replacement therapy, thus reinforcing the long-term economic advantage of transplantation over dialysis for the healthcare sector (84).

Table 62: Cost of dialysis-related adverse events

Dialysis AEs		Risk per cycle	Cost of AE (DKK)	Source/comment
All-cause cardiovascular events	PD	0.81%	DKK 84,139	Risk: Swai et al. (58,59); cost: DRG code 18MP02 (infectious or parasite-induced disease with dialysis)
	HD	1.22%		
All-cause infections	PD	1.26%	DKK 31,725	Risk: Swai et al. (58,59); cost: DRG code 05PR03 (heart failure, including cardiac shock, procedure group A)
	HD	1.23%		

8.6 Results

In this section, we present the results of the CU analysis for imlifidase compared to dialysis (standard of care). The overall approach to the model is to estimate the cost per QALY. We have estimated the ICER for imlifidase relative to the current standard of care.

8.6.1 Base case overview

Table 63 provides an overview of the base case used in the health economic model.

Table 63: Base case overview

Parameter	Used in model
Comparator	Dialysis (standard of care)
Type of model	Markov model
Time horizon	57 years (lifetime)
Treatment line	First-line (only available treatment)
Measurement and valuation of health effects	Health state utility values in the model were based on age-adjusted utility values from Lee et al. 2005 (56).
	Treatment / **HSUV**
	Transplanted patient with functioning graft / 0.71
	Haemodialysis / 0.44
	Peritoneal dialysis / 0.53
Included costs	We have included the following cost components in the model: Drug costs Hospital costs

	Costs of adverse events Terminal care costs Patient time and transportation costs
Dosage of pharmaceutical	Dose of imlifidase: [redacted]
Average time on treatment	[redacted] Comparator: ongoing until death. Median time until death: 19 years
Parametric function for graft survival	[redacted] Comparator: not relevant
Parametric function for survival with a functioning graft	[redacted] Comparator: not relevant

8.6.2 Base case results

In this section, we present the results of the CU analysis for imlifidase compared to dialysis (standard of care).

The QALYs associated with imlifidase are 8.39, and the total cost per patient treated with imlifidase is DKK 5,649,964. The QALYs associated with dialysis are 4.81, and the total cost per patient treated with dialysis is DKK 5,494,116. The modelled time horizon was 57 years.

Our results suggest that treatment with imlifidase and subsequent transplantation of patients with CKD who are highly sensitised and unlikely to receive a compatible donor organ is associated with an 74% increase in QALY whilst only causing a minimal increase in the estimated cost per patient of DKK 155,849. This implies an estimated ICER of DKK 43,597 per QALY.

Table 64: Base case results

Per patient	Imlifidase	Dialysis	Difference
Mean life years gained (discounted)			
Life years with functioning graft	9.45	0.34	9.11
Life years with dialysis	3.59	9.93	-6.34
Total life years	**13.04**	**10.27**	**2.77**
QALYs (discounted)			

Per patient	Imlifidase	Dialysis	Difference
QALYs with functioning graft	6.75	0.24	6.51
QALYs with dialysis	1.64	4.57	-2.94
Total QALYs	**8.39**	**4.81**	**3.57**
Costs (discounted)			
Drug costs	DKK 2,984,054	DKK 18,308	DKK 2,965,746
Imlifidase AEs	DKK 6,615	DKK 0	DKK 6,615
Health state: functioning graft	DKK 562,008	DKK 22,669	DKK 539,339
End-of-life costs	DKK 38,739	DKK 46,217	DKK -7,477
Health state: dialysis	DKK 1,434,619	DKK 3,964,774	DKK -2,530,155
Transportation	DKK 67,223	DKK 163,802	DKK -96,579
Patient time	DKK 556,706	DKK 1,278,347	DKK -721,641
Total costs	**DKK 5,649,964**	**DKK 5,494,116**	**DKK 155,849**
ICER			
Incremental results	Imlifidase vs dialysis		
ICER (per QALY)	DKK 43,597		

8.7 Sensitivity analyses

8.7.1 One-way sensitivity analyses

Uncertainty in the input parameters in the health economic model has been explored through extensive sensitivity analyses. Functionality is included in the model to enable input parameters to be varied systematically in order to evaluate their influence on the ICER.

In the deterministic sensitivity analyses, all input parameters included in the OWSA were adjusted by using the 95% confidence interval (CI), except for parameters related to the amount of imlifidase vials needed before transplantation could be performed and the proportion of female patients in the model. All CI were calculated based on the standard error (SE) or sourced directly from the applied study. In cases where no SE were available, we assumed that SE was 10% of the base case. In relation to the parameter related to the amount of imlifidase vials needed, the Danish clinical expert informed us that the patients in Danish clinical practice may be heavier compared to the imlifidase studies. We were informed that 20% of patients might be a realistic estimate of the percentage of patients being heavier than 88 kg and thus requiring three vials of imlifidase. In the OWSA, the upper bound case for patients requiring three vials

reflects this estimation. In the OWSA the proportion of patients receiving either one, two or three vials always sums to 100%. As such, when one parameter increases, the two others decrease. In relation to the parameter related to the proportion of female patients in the model, we were informed that 60% of patients might be a realistic estimate of the percentage of female patients. In the OWSA, the upper bound case for female patients reflects this estimation (60).

In Table 65, we present the results of the OSWA for the 13 most influential parameters. Figure 15 illustrates the results from the OWSA in a tornado diagram. Finally, Figure 16 presents the ICER estimated with different discount rates on imlifidase (varying from 0% to 100%).

Table 65: One-way sensitivity analyses results

Parameter	Rationale/ Source	Base case	Lower value	Upper value	ICER lower bound case (DKK)	ICER upper bound case (DKK)
Base case result (ICER)			Dominant			
Cost of dialysis per cycle	95% CI	DKK 198,042	DKK 159,226	DKK 236,858	181,223	-94,029
Death: from dialysis: HR vs Transplant, Chaundry 2022	95% CI	2.04	1.67	2.50	-85,946	147,132
Proportion of haemodialysis patients	95% CI	80.4%	64.6%	96.1%	152,549	-59,949
Cost of patient time per cycle: dialysis	95% CI	DKK 64,092	DKK 51,530	DKK 76,654	88,137	-943
Treatment distribution: patients requiring 3 vials	Danish clinical expert (60)	[redacted]	[redacted]	[redacted]	19,432	67,762
Transplant immunosuppressant costs (sub years)	95% CI	DKK 26,524	DKK 21,325	DKK 31,723	19,766	67,428
Cost: transplant procedure cost	95% CI	DKK 302,156	DKK 242,933	DKK 361,379	27,320	59,873
Treatment distribution: patients requiring 2 vials	Danish clinical expert (60)	[redacted]	[redacted]	[redacted]	55,265	31,928
Proportion requiring a second dose	95% CI	6.5%	[redacted]%	7.8%	35,727	52,209
Cost of ABMR	95% CI	DKK 339,084	DKK 272,623	DKK 405,544	36,394	50,799
Transplant AE: ABMR (Cycle 1)	95% CI	38.5%	31.1%	46.1%	36,969	50,470

Parameter	Rationale/ Source	Base case	Lower value	Upper value	ICER lower bound case (DKK)	ICER upper bound case (DKK)
Initial age (years)	95% CI	[redacted]	[redacted]	[redacted]	49,754	36,471
Cost of transportation: dialysis	95% CI	DKK 8,214	DKK 6,604	DKK 9,824	49,305	37,889

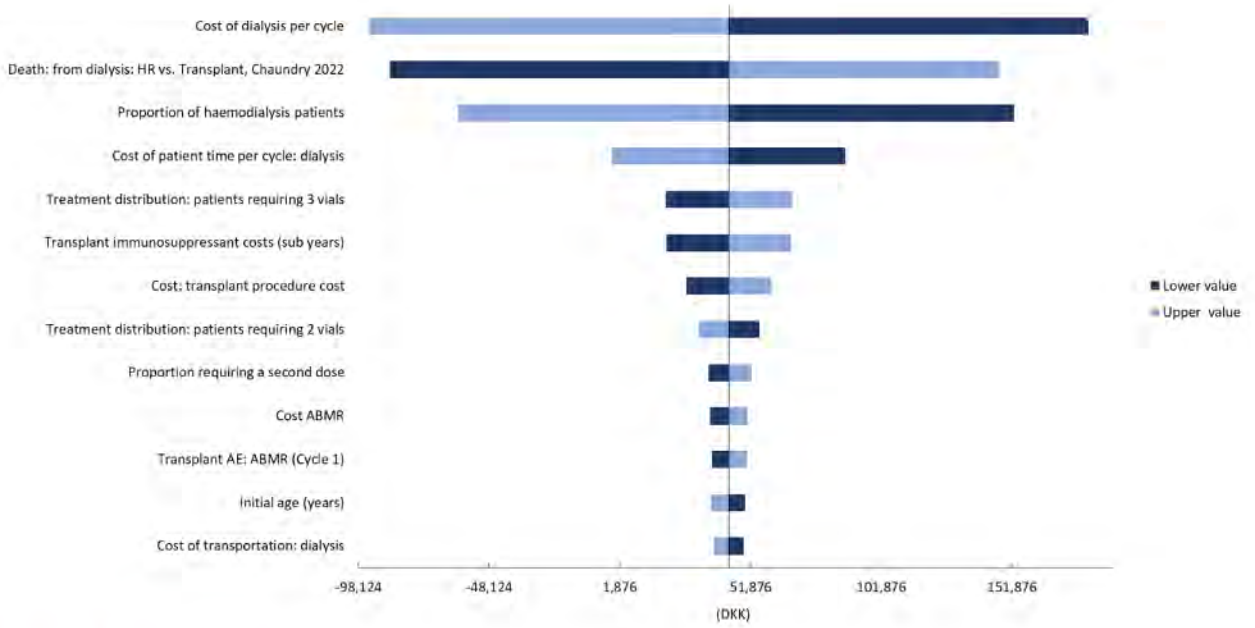

Figure 15: Tornado diagram

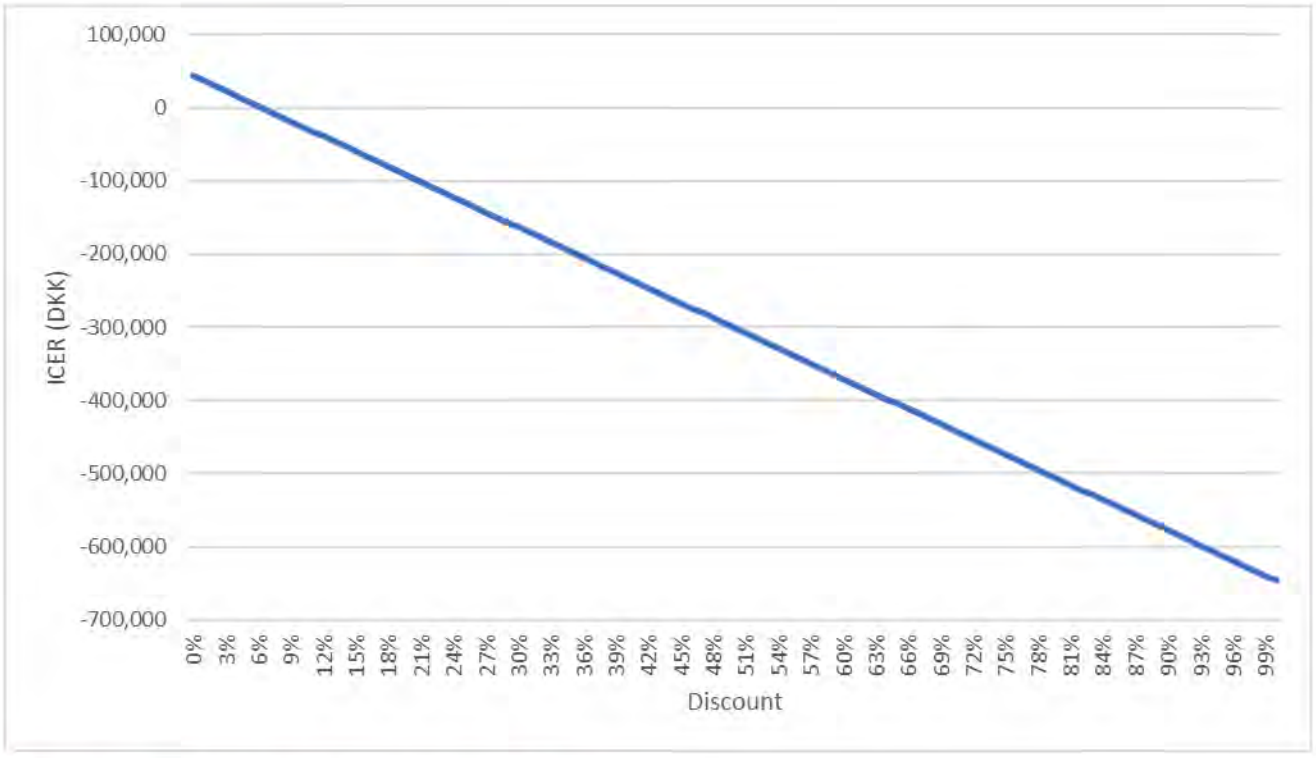

Figure 16: ICERs estimated with discount rates on imlifidase

8.7.2 Scenario analyses

In addition to the OWSA in the section above, several different scenarios are also explored. These scenarios are used to illustrate the sensitivity of the base case result to alternative specifications. These specifications, and their resulting ICER estimates, are presented in Table 66. As mentioned in section 4, a scenario analysis was included in which the patient survival with a functioning graft and dialysis was estimated based on transplantation mortality rates from Boenink 2020 (7) (scenario 9). The rationale for including the scenario analysis can be found in section 4. The scenario analysis was included based on dialogue with the DMC, who also shared the Boenink 2020 article with Hansa Biopharma.

Table 66: Results from the scenario analyses

	Δ Disc LY	Δ Disc QALY	Δ Disc Costs (DKK)	Cost/LY (DKK)	Cost/QALY (DKK)	Difference from baseline
Base case	2.77	3.57	155,849	56,223	43,597	
Scenario 1: Time horizon 10 years	0.85	1.96	539,251	637,507	275,788	533%
Scenario 2: Time horizon 20 years	1.82	2.90	108,101	59,544	37,247	-15%
Scenario 3: Utilities, Eriksen et al. 2017	2.77	3.11	155,849	56,223	50,087	15%
Scenario 4: Dialysis survival, Sørensen et al. 2016	3.75	4.03	683,615	182,133	169,781	289%
Scenario 5: Graft Loss extrapolations, iBox	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Graft Loss extrapolations, UT	2.79	3.59	139,288	49,997	38,760	-11%
Scenario 7: Survival extrapolations, UT	2.88	3.16	1,116,507	387,666	353,421	711%
Scenario 8: 2.1% (1/47) of the imlifidase-treated patients in the clinical setting do not undergo transplantation	2.71	3.50	206,813	76,290	59,158	36%
Scenario 9: Survival with a functioning graft and dialysis based on transplantation survival rates from Boenink 2020	0	2.25	-2,931,938	NA	-537,824	-1,334%

Abbreviations: UT: unlikely to be transplanted.

8.7.3 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the variables included in the CU model, a PSA was undertaken using 1,000 iterations. Several parameters in the model are not necessarily fixed values but possess a certain variability. This variability can be due to variations in the population with respect to the outcome, heterogeneity of the population and/or incomplete knowledge of the model parameters. This variability can be approximated through a PSA. This allows the CU model not only to evaluate the deterministic base case but also to see how the economic results might vary if several parameters of the models are varied simultaneously.

Table 67 presents the average and median ICER along with 95% confidence intervals from the PSA. Finally, Figure 17 and Figure 18 present the ICER scatter plot and imlifidase's cost-effectiveness acceptability curve. The specifications of the PSA are shown in Appendix J.

Table 67: PSA results

	Cost (DKK)			QALY			
	Imlifidase and transplant	Dialysis	Incremental	Imlifidase and transplant	Dialysis	Incremental	ICER (DKK/QALY)
Base case	5,649,964	5,494,116	155,849	8.4	4.8	3.6	43,597
PSA median	5,402,377	5,436,933	139,209	8.3	4.8	3.4	40,835
PSA mean	5,519,207	5,447,093	72,114	8.2	4.7	3.4	21,132
PSA 95% CI lower	3,724,890	2,254,700	-2,165,441	4.5	2.0	2.1	-1,054,472
PSA 95% CI upper	7,820,562	8,880,802	1,959,697	11.3	7.5	4.7	414,709

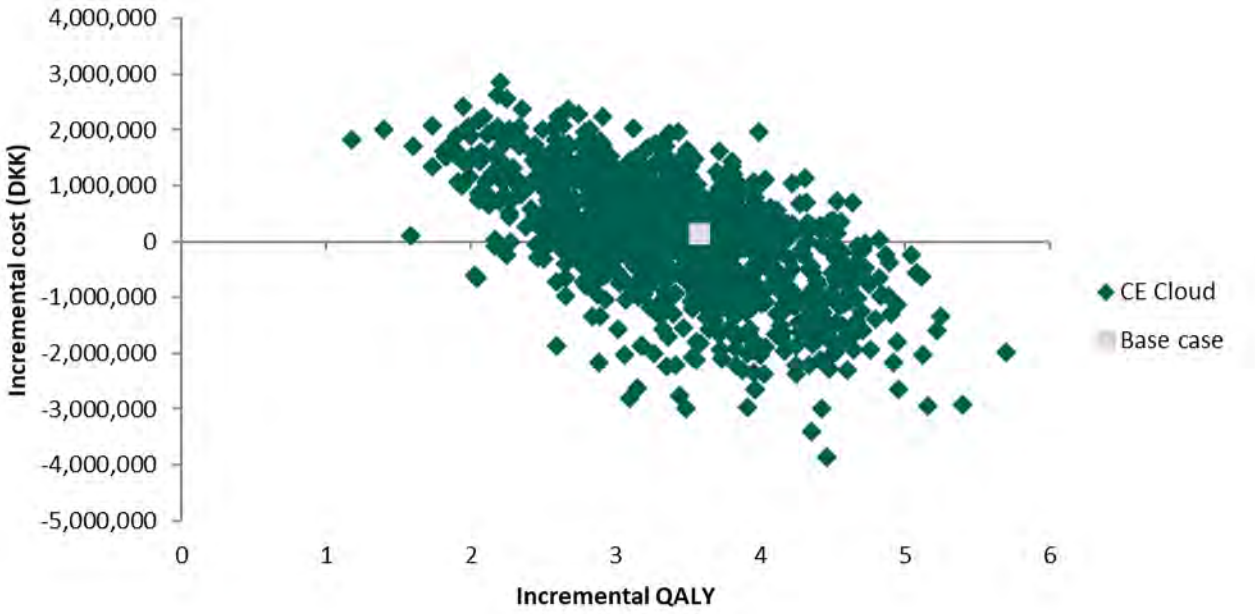

Figure 17: Imlifidase ICER scatter plot

Figure 18: Imlifidase cost-effectiveness acceptability curve

9. Budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending imlifidase as the standard desensitisation treatment for highly sensitised patients in Danish hospitals. The budget impact is estimated per year in the first five years after the recommendation of imlifidase.

The budget impact analysis compares the costs for the Danish regions in the scenario where imlifidase is recommended as standard treatment and the scenario where imlifidase is not recommended. The total budget impact per year is the difference between the two scenarios.

Number of patients

According to Scandiatransplant numbers from Q1 of 2022, around 514 Danish patients are on the waiting list to receive a new kidney (32). Based on a dialogue with the DMC, we assume that approximately 10% of these patients are sensitised, corresponding to 51 patients. We consulted a Danish clinical expert on the number of patients in Denmark who are highly sensitised and currently unlikely to be transplanted under STAMP/LAMP, and who are therefore potential candidates for imlifidase. We were informed that approximately [redacted] (corresponding to [redacted] Danish patients) are unlikely to receive a kidney under STAMP/LAMP. According to the clinical expert, the number of highly sensitised patients waiting for a kidney has accumulated on the waiting list, resulting in the number of patients being higher the first year after recommendation compared to the following years. Due to the limited size of the population, the assumption is that prevalence of new highly sensitised patients is somewhat constant. The clinical expert informed that [redacted] patients are a realistic number of new highly sensitised patients each year; thus in the budget impact analysis, we assumed that seven new patients who are unlikely to receive a transplant enter the waiting list each year. The number of patients expected to be treated with imlifased given a positve or negative recommendation are shown in Table 68 and Table 69.

Table 68: Number of patients expected to be treated over the next five-year period – if imlifidase is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Imlifidase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis	0	0	0	0	0
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 69: Number of patients expected to be treated over the next five-year period - if imlifidase is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Imlifidase	0	0	0	0	0
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Expenditure per patient

The cost-per-patient estimates applied in the budget impact analysis were based on the undiscounted cost estimates from the cost-per-patient analysis, excluding patient and transportation costs. These are presented separately for patients treated with imlifidase and dialysis in Table 70 and Table 71. To show the long-term budgetary benefits of imlifidase, we also included the total yearly costs of patients treated with imlifidase and dialysis up until year 11, when the imlifidase treatment beings to be cost-saving (Table 72).

Table 70: Cost per patient per year – patient treated with imlifidase

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs (DKK)	2,534,414	47,913	44,761	41,815	39,064
Hospital sector costs (DKK)	499,920	32,374	43,682	53,604	62,130

Table 71: Costs per patient per year – patient NOT treated with imlifidase

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs (DKK)	673	1,580	1,781	1,665	1,555
Hospital sector costs (DKK)	396,717	364,244	336,078	316,706	298,737

Table 72: Total cost per patient per year for patients treated with imlifidase and dialysis (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Year 11
Imlifidase	3,034,334	80,287	88,443	95,420	101,194	105,889	109,615	112,475	114,562	115,961	116,749
Dialysis	397,390	365,824	337,860	318,371	300,293	283,267	267,202	252,045	237,745	224,253	211,524
Accumulated increment	2,636,945	2,351,408	2,101,991	1,879,040	1,679,941	1,502,564	1,344,977	1,205,407	1,082,224	973,932	879,157

Budget impact

Below, we present the results of the budget impact analysis in the first five years with and without a recommendation of imlifidase.

The budget impact of recommending imlifidase as standard treatment for highly sensitised dialysis patients who are unlikely to receive a kidney is DKK [redacted] in the first year and DKK [redacted] in year 5. The total five-year budget impact is DKK [redacted]. In Table 73 the budget impact in each year is presented.

Table 73: Expected budget impact of recommending imlifidase for highly sensitised dialysis patients who are unlikely to receive a kidney through prioritisation programmes

	Year 1	Year 2	Year 3	Year 4	Year 5
Imlifidase is recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: drug costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Of which: hospital costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imlifidase is NOT recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: drug costs (DKK)	6,727	20,506	33,580	44,883	55,440
Of which: hospital costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In relation to the budget impact analysis, we also undertook a scenario analysis in which we assumed that there are 50% fewer patients and 50% more patients compared to the base case analysis. The results from this analysis are shown in Table 74.

Table 74: Budget impact sensitivity

Year	Base case (DKK)	Lower bound case (DKK) (-50% patients)	Upper bound case (DKK) (+50% patients)
Year 1	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]

10. Discussion of the submitted documentation

The introduction of imlifidase opens up the possibility of kidney transplantation in patients who would otherwise not be eligible for transplantation. The majority of Danish ESRD patients have access to kidney transplantation. Imlifidase improves equity in the access to kidney transplants by allowing the small set of patients who are still dependent on lifetime dialysis today to undergo this life-changing procedure with enormous quality-of-life implications. Thus, imlifidase plays an important role for highly sensitised adult CKD patients. SoC in these highly sensitised patients is dialysis and the time on dialysis substantially impacts patients' QoL and survival. Moreover, dialysis is associated with many complications and side effects which get worse with time on dialysis. Death rates for patients at high immunologic risk remaining on dialysis are consistently higher than for patients who undergo desensitisation and transplantation.

The four phase II studies (Study 02, Study 03, Study 04 and Study 06) and the long-term Study 14 were uncontrolled, as double-blind, randomised, controlled study design was not feasible and ethical, since it would require randomisation of patients to a known non-satisfactory comparator (as no other desensitisation therapy exists). In all four phase II studies, the sample size was small and not based on formal statistical considerations. To accommodate this limitation, we provided estimates from a pooled analysis including Study 02, 03, 04 and 06. Results from Study 14, which is a long-term study with results from all transplanted patients from Study 02, 03, 04 and 06, were also presented.

Results from the clinical studies (Study 02, 03, 04, 06 and 14) demonstrated the clinical efficacy of imlifidase in terms of DSA elimination and crossmatch conversion, kidney function, graft survival, overall survival and QoL. The clinical studies showed that all patients received a crossmatch conversion following treatment with imlifidase that the kidney function was good or satisfactory six months after imlifidase and transplant, and that graft survival was 90% three years after transplant. At the time of the current analysis, five-year data was only available for a few patients but in the patients with five-year data, graft survival was [redacted]

The base case of the CU analysis showed that the QALYs associated with imlifidase are 8.39 and the total cost per patient treated is DKK 5,649,964. The QALYs associated with dialysis are 4.68, and the total cost per patient is DKK 5,494,116. This leads us to the conclusion that treatment with imlifidase is the cost-effective treatment strategy compared to dialysis.

Several sensitivity analyses were undertaken to investigate the robustness of the base case result. In the OWSA, we found that some parameters could influence the results by a rather large margin. The parameters that were the most influential were the assumed cost of dialysis per cycle, The HR of death for dialysis vs transplanted patients and the proportion of haemodialysis patients.

Several scenario analyses were also undertaken to investigate the result using alternative model specifications. These results highlight the fact that assumptions made regarding overall survival when treatment with dialysis, graft survival and survival with a functioning graft are of key importance for the analysis. When looking at the data, it becomes clear that the extrapolations of graft survival and survival with a functioning graft based on the sample of patients classified as "unlikely to be transplanted" were by far the most conservative, suggesting that the data for this extrapolation may not have been representative of the population.

The yearly report from the Danish Nephrology Registry from 2017 holds data on patient survival after the first renal transplantation (deceased donor), by time of transplantation, 1990-2017. From the figure 4.4 in the report, it is seen that overall patient survival in patients who have received kidney transplantation from a deceased donor during the

period from 2005-2009 (the most recent data with 10 years of follow up) is between 85-90% and 70-75% for 5-years and 10-years respectively. In comparison, the model extrapolation predicts survival with a functioning graft to be 86.5% and 74.8% after 5 and 10 years and overall survival to be 85.4% and 71.2% after 5 and 10 years, respectively. Based on this, we conclude that the extrapolations applied in the health economic model are in line with the expected survival in the relevant Danish patient population.

The PSA showed that the combined uncertainty of all model input parameters in most of the iterations did not change the outcome of the cost-effectiveness analysis (77.3% of iterations with a WTP of DKK 300,000).

The budget impact analysis assumed that 10 patients are eligible for treatment with imlifidase the first year after recommendation, dropping to seven patients a year in the following years. The budget impact of recommending imlifidase for the treatment of highly sensitised patients who are unlikely to be transplanted is approximately DKK 26.4 million in the first year and DKK [redacted].2 million in year 5. The reason the budget impact of introducing imlifidase is positive is the substantial start-up costs related to the imlifidase treatment. In the long term, however, imlifidase would become cheaper compared to dialysis, but this is not shown because the timespan of the budget impact analysis (BIA) is only five years. Based on this, we presented the accumulated incremental cost over 11 years in Table 72, which points out the stark reduction in incremental costs over time for patients receiving imlifidase and subsequent transplantation.

There is a larger uncertainty regarding the size and demographic characteristics of the patients eligible for treatment with imlifidase, given the small number of patients this would involve. The number of patients was estimated based on clinical input, and it is likely that our budget impact analysis is associated with large uncertainties, as just a small change in the number of patients changes the budget impact considerably.

The survival of highly sensitised patients who are transplanted compared to those who stay on dialysis has been discussed with the DMC. The DMC has argued that survival is expected to be similar between highly sensitised transplanted patients if compared to a similar patient population who remain in dialysis treatment with reference to the study by Manook et al. 2017 (4). Manook et al. 2017 compared the survival of patients opting for an HLAi kidney transplant with that of similarly sensitised patients awaiting a compatible organ (while being on dialysis). Manook et al. 2017 reported no difference in survival of sensitised patients undergoing HLAi transplantation compared with those on dialysis awaiting a compatible organ, many of whom are unlikely to receive a transplant.

It should be noted that only a very small number of patients were observed beyond four years, and Manook et al. 2017 can therefore not be used as a reliable long-term study. In addition, there is a large amount of literature stating the opposite, i.e., that a similar patient population on dialysis does not have a patient survival similar to highly sensitised transplanted patients. The dialysis mortality is worse than transplantation, even in the population of dialysis patients who are fit for transplant and on the transplant waiting list. Figure 1 presents Kaplan-Meier estimates of patient survival from the 2020 annual report form the Norwegian Renal Registry. The Norwegian Renal Registry is an epidemiology quality register for patients with severe renal disease and follows patients for their entire life course. As seen in Figure 1, the patient survival for patients receiving a transplantation is much higher compared to patients who remain on dialysis – a survival benefit that is present in both the population with patients who are candidates for a transplantation and who are not candidates for a transplantation. In addition, the 2018 ERA-EDTA Registry Annual Report (6) presents an adjusted five-year patient survival for deceased donor transplantation of 92.0% (95% CI 91.7–92.3), while an unadjusted five-year patient survival for dialysis is 42.6% (95% CI 42.5–42.7). The real-world data from the Norwegian Renal Registry and the ERA-EDTA Registry demonstrates that there is a survival difference in patients being transplanted and patients receiving dialysis in favour of transplantation.

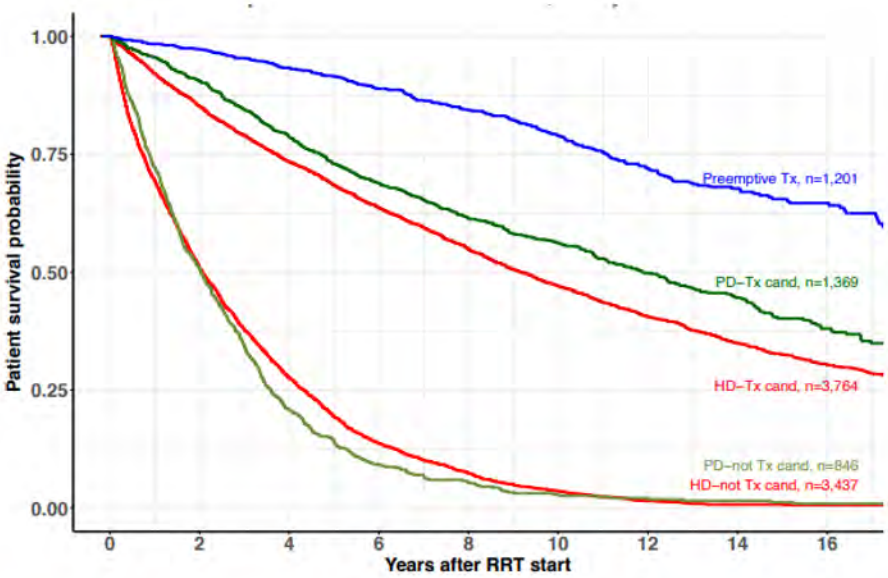

Figure 19: Patient survival in renal replacement therapy (RRT) by transplantation assessment and 1st treatment, Norway 2000–2020. Source: Annual report from the Norwegian Renal Registry 2020 (5).

11. List of experts

We consulted a Danish clinical expert (MD, PhD) who specialises in nephrology and renal transplantations. The clinical expert wanted to be anonymous; therefore, we did not publish the name of the expert.

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

This appendix describes how the literature searches for identifying evidence on efficacy and safety for imlifidase and dialyses were performed. For this application, we performed three separate systematic literature searches: one to inform the efficacy and safety of imlifidase, one to inform QoL and survival of dialysis and one to inform safety in dialysis. Below, we list the objective of the literature searches and describe the applied databases, registers etc. Then, we describe the development of the search strategies and search strings and specify the inclusion and exclusion criteria for the searches, followed by a description of the systematic selection of studies and reasons for exclusion of full-text articles. Finally, we describe the strengths and weaknesses of the performed literature searches and address the quality of unpublished data.

Efficacy and safety of imlifidase

Objective of the literature search

The objective of the literature search was to address the efficacy and safety of imlifidase in adults with CKD, including:

- efficacy on DSA elimination and crossmatch conversion;
- kidney function;
- graft survival;
- overall survival;
- HRQoL; and
- AEs.

Data sources

We searched for relevant literature in the databases Medline (via the PubMed platform) and Embase (via the Ovid platform) on 5 May 2022 (Table 75). Moreover, we searched the US NIH registry & results database and the EU Clinical Trials Register for ongoing trials on imlifidase in the relevant population (adults with CKD undergoing kidney transplants) (see Table 76). We did not search specifically for any conference material.

We searched for ongoing trials by searching for interventional studies, including imlifidase in kidney transplant patients. In the US NIH registry & results database, we excluded studies with the recruitment status of Suspended, Terminated, Completed or Withdrawn. In the EU Clinical Trials Register, we excluded studies with the Trial Protocol status of: Completed or Prematurely Ended. The searches were completed on 3 May 2022.

Table 75: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search
Embase	Ovid	Up until today	05.05.2022
Medline	PubMed	Up until today	05.05.2022

Table 76: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	We searched for ongoing trials including imlifidase. We excluded studies with the recruitment status of: Suspended, Terminated, Completed or Withdrawn. And excluded studies that did not include kidney transplant patients.	03.05.2022
EU Clinical Trials Register	EU Clinical Trials Register	We searched for ongoing trials, including imlifidase. We excluded studies with the End of Trial Status: Completed or Prematurely Ended. And excluded studies that did not include kidney transplant patients.	03.05.2022

The search in the US NIH registry & results database resulted in three relevant ongoing trials, and the search in the EU Clinical Trials Register resulted in one relevant ongoing trial. In Table 77, the four trials are listed, including information on the NCT/ECT number, title, the estimated study completion and the primary objective for each study as it is described in the US NIH registry & results database and the EU Clinical Trials Register.

Table 77: Ongoing trials registered in US NIH registry results

NCT/ECT number	Trial name	Expected study completion	Primary objective and outcome
ECT 2021-002640-70	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	Not registered	To determine the one-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.
NCT05049850	An Open Label, Phase II Study to Investigate DSA Rebound in Patients With a Positive Crossmatch, Made Transplantable With Imlifidase	March 2023	To determine the proportion of patients with DSA rebound.
NCT03611621	A Prospective Observational, Long Term Follow up Study of Patients Treated With Imlifidase Prior to Kidney Transplantation	December 2022	To evaluate graft survival in subjects who have undergone kidney transplantation after imlifidase administration
NCT04935177	An Open-label, Controlled, Randomized Phase 3 Trial Evaluating 12-month Kidney Function in Highly Sensitized (cPRA ≥99.9%) Kidney Tx Patients With Positive XM Against a Deceased Donor, Comparing Desensitization Using Imlifidase With SoC	December 2023	To evaluate graft survival in subjects who have undergone kidney transplantation after imlifidase administration

Supplementary manual searches

We searched for the EPAR for the intervention. The EPAR for imlifidase is available and last updated on 31 August 2021.

Search strategy

The search strings used to identify relevant publications presenting efficacy and safety data for imlifidase combined MESH terms and free search terms containing alternative spelling and names representing the diagnosis ESRD, the intervention and relevant outcomes such as efficacy, survival, graft function, HRQoL and AEs. The syntax, the included search terms and the retrieved hits at each state are presented in Table 78 and Table 79 for the Medline and Embase search, respectively.

Table 78: Medline search strategy

No.	Query	Hits
1	(((((chronic renal failure[MeSH Terms]) OR chronic renal insufficiency[MeSH Terms]) OR end stage kidney disease[MeSH Terms]) OR end stage renal disease[MeSH Terms]) OR end stage renal failure[MeSH Terms]) OR ("chronic renal failure"[Title/Abstract] OR CRF[Title/Abstract] OR "chronic renal insufficiency"[Title/Abstract] OR "end stage kidney disease"[Title/Abstract] OR ESKD[Title/Abstract] OR "end stage renal disease"[Title/Abstract] OR ESRD[Title/Abstract] OR "end stage renal failure"[Title/Abstract] OR ESRF[Title/Abstract] OR "chronic kidney disease"[Title/Abstract] OR CKD[Title/Abstract] OR "chronic kidney failure"[Title/Abstract] OR CKF[Title/Abstract] OR "established renal failure"[Title/Abstract])	201,545
2	kidney transplantation[MeSH Terms]	102,346
3	(((kidney[Title/Abstract] OR renal[Title/Abstract]))) AND (((allograft[MeSH Terms]) OR allogeneic transplantation[MeSH Terms]) OR (allograft*[Title/Abstract] OR transplant*[Title/Abstract] OR graft*[Title/Abstract] OR allogen*[Title/Abstract]))	136,866
4	2 OR 3	155,469
5	1 OR 4	32,535
6	(((histocompatibility[MeSH Terms]) OR histocompatibility antigens[MeSH Terms]) OR histocompatibility testing[MeSH Terms]) OR hla antigens[MeSH Terms]	194,651
7	(Histocompat*[Title/Abstract] OR HLA[Title/Abstract] OR "human leukocyte antigen"[Title/Abstract] OR "human leucocyte antigen"[Title/Abstract] OR anti-HLA[Title/Abstract] OR "donor specific antibody"[Title/Abstract] OR "donor specific antibodies"[Title/Abstract] OR DSA[Title/Abstract] OR "calculated relative frequency"[Title/Abstract] OR cRF[Title/Abstract] OR "calculated panel reactive antibody"[Title/Abstract] OR cPRA[Title/Abstract] OR "panel reactive antibody"[Title/Abstract] OR PRA[Title/Abstract] OR "taux de greffons incompatibles"[Title/Abstract] OR TGI[Title/Abstract])	178,376
8	(immunologic desensitization[MeSH Terms]) OR (Desensiti*[Title/Abstract] OR sensiti*[Title/Abstract] OR allosensiti*[Title/Abstract] OR hypersensiti*[Title/Abstract] OR alloimmuni*[Title/Abstract] OR hyperimmuni*[Title/Abstract] OR incompatib*[Title/Abstract] OR crossmatch*[Title/Abstract] OR mismatch*[Title/Abstract])	185,7209
9	6 OR 7 OR 8	210,7541

No.	Query	Hits
10	5 AND 9	45,623
11	(Imlifidase[Title/Abstract] OR IdeS[Title/Abstract] OR HMed-IdeS[Title/Abstract] OR "IgG-degrading enzyme of Streptococcus pyogenes"[Title/Abstract] OR Idefirix[Title/Abstract] OR IgG Endopeptidase[Title/Abstract] OR "IgG inactivating agent"[Title/Abstract] OR "IgG inactivating agents"[Title/Abstract])	620
12	10 AND 11	15
13	(Efficac*[Title/Abstract] OR effective*[Title/Abstract])	2,981,732
14	((Transplant*[Title/Abstract] OR treatment[Title/Abstract])) AND (rate[Title/Abstract] OR rates[Title/Abstract] OR success[Title/Abstract] OR successes[Title/Abstract])	877,112
15	(graft survival[MeSH Terms]) OR graft rejection[MeSH Terms]	99,708
16	((Allograft[Title/Abstract] OR Graft[Title/Abstract] OR patient[Title/Abstract] OR posttransplant[Title/Abstract] OR post-transplant[Title/Abstract])) AND (survival[Title/Abstract] OR function[Title/Abstract] OR failure[Title/Abstract] OR rejection[Title/Abstract] OR loss[Title/Abstract])	699,131
17	(delayed graft function[MeSH Terms]) OR ("Antibody mediated rejection"[Title/Abstract] OR AMR[Title/Abstract] OR ABMR[Title/Abstract] OR "delayed graft function"[Title/Abstract] OR "acute rejection"[Title/Abstract] OR "biopsy confirmed acute rejection"[Title/Abstract] OR BCAR[Title/Abstract])	27,034
18	((adverse drug event[MeSH Terms]) OR adverse drug reaction[MeSH Terms]) OR ("Adverse event"[Title/Abstract] OR "adverse events"[Title/Abstract] OR "adverse reaction"[Title/Abstract] OR "adverse reactions"[Title/Abstract] OR "side effect"[Title/Abstract] OR "side effects"[Title/Abstract] OR safety[Title/Abstract] OR tolerability[Title/Abstract] OR discontinu*[Title/Abstract])	1,221,262
19	("Survival"[Mesh] OR "Mortality"[Mesh] OR "mortality" [Subheading]) OR (survival[Title/Abstract] OR mortality[Title/Abstract]) OR (quality of life[MeSH Terms]) OR ("Quality of life"[Title/Abstract] OR QoL[Title/Abstract] OR HRQoL[Title/Abstract] OR KDQOL[Title/Abstract]) OR ("Kidney Disease Quality of Life"[Title/Abstract])	2,482,064
20	13 – 19 OR	6,364.094
21	12 AND 20	13

Table 79: Embase search strategy

No.	Query	Hits
1	(chronic kidney failure OR end stage renal disease).sh	158,749

No.	Query	Hits
2	("chronic kidney failure" OR "chronic renal failure" OR CRF OR "chronic renal insufficiency" OR "end stage kidney disease" OR ESKD OR "end stage renal disease" OR ESRD OR "end stage renal failure" OR ESRF OR "chronic kidney disease" OR CKD OR "chronic kidney failure" OR CKF OR "established renal failure").ti,ab	227,857
3	1 OR 2	278,731
4	(kidney transplantation OR renal replacement therapy).sh	171,934
5	(kidney OR renal).ti,ab	1,247,314
6	(allograft* OR transplant* OR graft* OR allogen*).ti,ab	1,113,971
7	(allograft OR allotransplantation).sh	59,866
8	4 – 7 OR	2,183,927
9	3 OR 8	2,232,712
10	(major histocompatibility complex OR HLA antigen).sh	60,281
11	(Histocompat* OR HLA OR "human leukocyte antigen" OR "human leucocyte antigen" OR anti-HLA OR "donor specific antibody" OR "donor specific antibodies" OR DSA OR "calculated relative frequency" OR cRF OR "calculated panel reactive antibody" OR cPRA OR "panel reactive antibody" OR PRA OR "taux de greffons incompatibles" OR TGI).ti,ab	250,065
12	(Desensiti* OR sensiti* OR allosensiti* OR hypersensiti* OR alloimmuni* OR hyperimmuni* OR incompatib* OR crossmatch* OR mismatch*).ti,ab	2,309,322
13	(desensitization).sh	23,901
14	10 - 13 OR	2,546,351
15	9 AND 14	226,371
16	(Imlifidase OR IdeS OR HMed-IdeS OR "IgG-degrading enzyme of Streptococcus pyogenes" OR Idefirix OR IgG Endopeptidase OR "IgG inactivating agent" OR "IgG inactivating agents").ti,ab	874
17	15 AND 16	61
18	(Efficac* OR effective*).ti,ab	3,990,716
19	(Transplant* OR treatment).ti,ab	7,156,115
20	(rate OR rates OR success OR successes).ti,ab	4,487,421
21	(19 AND 20)	1,387,107

No.	Query	Hits
22	(Graft survival OR graft rejection OR kidney allograft rejection OR kidney graft rejection).sh	137,908
23	(Allograft OR Graft OR patient OR posttransplant OR post-transplant).ti,ab	4,169,305
24	(survival OR function OR failure OR rejection OR loss).ti,ab	6,141,120
25	(23 AND 24)	1,164,648
26	("Antibody mediated rejection" OR AMR OR ABMR OR "delayed graft function" OR "acute rejection" OR "biopsy confirmed acute rejection" OR BCAR).ti,ab	46,057
27	(delayed graft function).sh	7,431
28	(adverse drug reaction).sh	265,006
29	("Adverse event" OR "adverse events" OR "adverse reaction" OR "adverse reactions" OR "side effect" OR "side effects" OR safety OR tolerability OR discontinu*).ti,ab	1,681,155
30	exp mortality/ or exp disease free survival/ or exp short term survival/ or exp survival/ or exp overall survival/	2,277,282
31	("survival" or "mortality").ti,ab.	2,655,822
32	(Quality of life).sh	552,461
33	("Quality of life" OR QoL OR HRQoL OR KDQOL OR "Kidney Disease Quality of Life").ti,ab	531,600
34	18 OR 21 OR 22 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33	8,947,514
35	17 AND 34	46
36	limit 35 to conference abstract status	27
37	35 NOT 36	19

Systematic selection of studies

The systematic selection of studies in the systematic literature search of efficacy and safety data on imlifidase followed the PICO framework are specified in Table 80. The criteria were developed to support the overall objective of the systematic literature search, and generally, we included studies in which adults with CKD were treated with imlifidase. We only included articles reporting results on one or more of the prespecified relevant outcomes, i.e., efficacy on DSA elimination and crossmatch conversion, kidney function (eGFR), death-censored graft survival rate, patient survival, HRQoL and AEs. Furthermore, we only included full-text publications.

Table 80: Inclusion and exclusion criteria in the literature search

Inclusion criteria	
Population	Adult people with CKD who have been transplanted or are awaiting a kidney transplant from a deceased donor, who have a positive crossmatch and are highly sensitised with HLA antibodies
Intervention/ comparators	Imlifidase/Idefirix®
Outcomes	Efficacy on DSA elimination and crossmatch conversion (ability to create a negative crossmatch test in people who exhibit donor specific antibodies), kidney function (eGFR), death-censored graft survival rate, patient survival, HRQoL and adverse events.
Study types	Meta-analyses, systematic literature reviews, RCTs, non-randomised studies, observational studies, cohort studies, databases and registers.
Language	English
Geographical	No geographical limit
Publication types	Not: Case reports and series, reviews, expert opinion, commentaries and letters, abstract only, conference poster, conference abstract.

The results of the literature search and the flow of studies through the review, including the applied exclusion reasons, are presented in Figure 20.

We identified 19 records in Embase and 13 records in Medline. A total of 27 records were identified after removal of duplicates. Of these, 20 records were excluded based on title/abstract screening, and an additional three records were excluded based on review at the full-text level, leaving four relevant studies for inclusion in the assessment.

Figure 20: PRISMA flow diagram for imlifidase search

Table 81 lists the three articles that were excluded after the full-text assessment, including an explanation as to why the articles was excluded.

Table 81: Publications excluded at full-text level

Author(s)	Year	Title	Reason for exclusion
Lorant et al.	2015	Rapid removal of anti-HLA antibodies in immunized patients awaiting renal transplantation-a dose finding study of the IGG degrading enzyme ides	Wrong publication type: Abstract
Lorant et al.	2016	Rapid removal of anti-HLA antibodies in immunized patients. Two dose finding studies of the IgG degrading enzyme IdeS	Wrong publication type: Conference abstract
Lonze et al.	2018	IdeS (imlifidase): A Novel Agent That Cleaves Human IgG and Permits Successful Kidney Transplantation Across High-strength Donor-specific Antibody	The study was registered with the NCT02790437 trial; however, only reported data from a single centre. Jordan et al. 2021 was also NCT02790437 and included all 19 participants from the trial. Therefore, we decided to use

Author(s)	Year	Title	Reason for exclusion
			Jordan et al. as our primary source.

The systematic literature search identified four relevant publications. Table 82 provides an overview of the four studies, including their aim, study design, patient population intervention and outcomes.

Table 82: Overview of studies included in the assessment

Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Lorant et al. 2018 (37), NCT02224820					
The purpose of this study was to evaluate the efficacy, safety, tolerability and pharmacokinetics of HMED-IdeS in sensitised patients with CKD. There was no intent to transplant.	Phase 2, uncontrolled, non-randomised single-centre trial	Adults diagnosed with CKD and in dialysis with identified antibodies against at least two HLA antigens, of which at least one is 3000 MFI or more as measured by SAB assay on at least two occasions.	IdeS® administered in ascending doses: 0.12 and 0.25 mg/kg once or twice within 48 hours. No comparator. Sample size: 8	The primary efficacy endpoint was the IdeS® dosing scheme in the majority of the patients resulting in human leucocyte antigen (HLA) antibody levels which are acceptable for transplantation, measured as mean fluorescent intensity (MFI) of less than 1100, within 24 hours from dosing. MFI was determined by single antigen bead (SAB) assay and detection of complement fixating ability (Clq Screen) in serum.	• The number of significant adverse events, all clinical laboratory tests, vital signs and ECG judged as clinically significant, reported at week 9 • The IgG cleavage and regeneration as measured by ELISA up to day 64 • The presence of Anti-Drug Antibodies formation in serum throughout a 64-day period • The IdeS® T1/2 in alpha phase up to day 21
Jordan et al. 2017 (38), NCT02475551					

Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
The purpose of this study was to assess the safety and efficacy of the IgG-degrading cysteine protease IdeS® in the transplantation setting.	Phase 2 uncontrolled, non-randomised single-group study in patients with CKD and intended for transplantation, with ≥1 identified HLA antibody with MFI ≥3000 DD, DL	Adults diagnosed with CKD and in dialysis with preformed anti-HLA antibodies (non-DSA, DSA or both), negative T-CDC CXM and at least one antibody MFI >3000	IdeS® as a single infusion: 0.25 and 0.5 mg/kg. No comparator. Sample size: 10	The primary safety endpoint was the adverse events, clinical laboratory tests, vital signs and ECGs within six months.	The secondary efficacy endpoint was the IdeS® dosing scheme resulting in anti-human leucocyte antigen (HLA) antibody levels which were acceptable for transplantation, measured as a mean fluorescent intensity (MFI) of less than 1100 as measured in a single antigen bead (SAB) assay within 24 hours from dosing.
Jordan et al. 2021 (39), NCT02790437					
The purpose of this study is to evaluate the effectiveness of the study drug IdeS in creating a negative crossmatch test (XM) in patients who are on the waiting list for a kidney transplant and have previously	Phase 2, uncontrolled, multi-centre, open-label single-group trial	Adults on the kidney transplant waiting list who have previously undergone desensitisation unsuccessfully, or for whom effective desensitisation is highly unlikely, and who have a	IdeS® as a single infusion: 0.25 mg/kg on study day 0. If negative crossmatch was not achieved, a second dose (0.25 mg/kg) was given within two days of the first infusion. Following IdeS® treatment,	The primary efficacy endpoint was the number of patients with crossmatch conversion from positive to negative within 24 hours of IdeS® dosing.	The secondary efficacy endpoints were: Number of patients with DSA with an MFI value >3000 within 180 days after administration of IdeS® Time to create a Negative CDC Crossmatch Test, defined as the first timepoint all CDC XM results were negative after administration of IdeS®. Time frame: 2h, 6h and 24h after administration of IdeS® Time to create a Negative FACS Crossmatch Test,

Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
undergone desensitisation unsuccessfully, or for whom effective desensitisation will be highly unlikely		live or deceased donor with a positive crossmatch test	participants underwent kidney transplantation. No comparator. Sample size: 19		defined as the first timepoint all FACS XM results were negative after administration of IdeS®. Time frame: 2h, 6h and 24h after administration of IdeS® Kidney function after IdeS® treatment assessed by eGFR calculated as described by the MDRD equation within 180 days after administration of IdeS® Serum IgG Concentration after administration of IdeS® within 180 days after administration of IdeS®. The IgG concentration measured for this outcome is the sum of intact and scIgG, because the assay used cannot discriminate between the two. The secondary pharmacokinetics endpoints, all measured pre-dose to day 14 after administration of IdeS® with non-compartmental PK analyses, were: Cmax (Maximum observed plasma concentration of IdeS®) Tmax (Time point for maximum observed plasma concentration of IdeS® following dosing) AUC (Area under the plasma concentration versus time curve)

Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
					t1/2 during both distribution and elimination phase CL (Clearance) Vss (Volume of distribution at steady state) Vz (Volume of distribution during the elimination phase)
Kjellman et al. 2021 (40), NCT03611621					
The purpose of this study is to collect data from extended follow-up in subjects that have received a kidney transplant following imlifidase dosing to provide a better understanding of the long-term outcome for these subjects.	A phase 2, prospective, observational, long-term follow-up study	Subjects that have participated, or are currently participating, in the imlifidase kidney transplantation studies: 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06	No active intervention was included, as the purpose of the study was to collect data on patients who have received a kidney transplant following imlifidase. Sample size: 39	The primary endpoint of this study is to determine overall graft survival in subjects who have undergone kidney transplantation after imlifidase administration, defined as time from transplantation to graft loss. Time frame: three years after first dose of imlifidase.	Time frame: three years after first dose of Idefirix® Overall patient survival defined as time from transplantation to death for any cause Evaluation of long-term kidney function assessed by eGFR Evaluation of long-term kidney function assessed by P-creatinine Evaluation of long-term kidney function assessed by proteinuria Evaluation of number of graft rejection episodes classified by Banff, Haas et al. 2018 Evaluation of graft rejection by recording graft rejection episodes treatments Evaluation of comorbidities in transplanted subjects Evaluation of treatments of comorbidities by record of concomitant immunosuppressive medication Assessment of blood hemoglobulin

Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
					Assessment of differential analysis of leucocyte Assessment of thrombocytes Assessment of total IgG levels Assessment of donor-specific antibodies (DSA) analysed by SAB-HLA Assessment of the presence of antibodies towards BK virus Assessment of the immunogenicity of imlifidase by analysing serum samples for anti-drug antibody (ADA) levels using an ImmunoCAP assay Evaluation of health-related quality of life with patient questionnaires EQ-5D-5L Evaluation of health-related quality of life with patient questionnaires KDQOL-SF

Adverse events associated with dialysis

Objective of the literature search

The objective of the literature search was to address the safety of dialysis in adults with CKD by establishing the adverse events associated with dialysis.

Data sources

We searched for relevant literature in the databases Medline (via the PubMed platform) and CENTRAL (via the Cochrane platform) on 8 July 2022 (Table 83). Moreover, we searched the International HTA database for records on dialysis (Table 84). We did not search specifically for any conference material.

We searched for records in the International HTA database by searching for dialysis and CKD. Records were excluded if they were from before 2012. The search was completed on 28 April 2022.

Table 83: Bibliographic databases included in the search

Database	Platform	Relevant period for the search	Date of search completion
CENTRAL	Cochrane	From 2017 and until today	08.07.2022
Medline	PubMed	From 2017 and until today	08.07.2022

Table 84: Database included in the search

Database	Platform	Search strategy	Date of search
International HTA database	https://database.inahta.org/	We searched for records, including dialysis and chronic kidney disease. We followed the PICO criteria (Table 87) and excluded records if they were from before 2012, did not include patients on dialysis and did not include any of the relevant outcomes (adverse events).	28.04.2022

The search in the International HTA database resulted in the identification of six records after excluding records from before 2012. Based on an initial screening of abstract/summary, four records were excluded because they did not include the relevant population. The remaining two records did not include any relevant outcomes. Thus, the search of the International HTA database did not identify any records relevant to this application.

Search strategy

The search strings used to identify relevant publications presenting adverse events associated with dialysis combined MESH terms and free-search terms containing alternative spelling and names representing the diagnosis CKD, the comparator (dialysis) and the relevant outcome. The syntax, the included search terms and the retrieved hits at each state are presented in Table 85 and Table 86 for the Medline and CENTRAL search, respectively.

The search strategy included publications from the last five years and meta-analysis or systematic literature reviews, as we wished to identify recent high-quality studies with many observations. The strategy initially focused on these studies but would be extended if no relevant studies were identified within the first search.

Table 85: Medline search strategy

No.	Query	Hits*
1	(end stage kidney disease[MeSH Terms] OR end stage renal disease[MeSH Terms] OR end stage renal failure[MeSH Terms] OR "chronic renal failure"[Title] OR "chronic renal insufficiency"[Title] OR "end stage kidney disease"[Title/Abstract] OR ESKD[Title/Abstract] OR "end stage renal disease"[Title/Abstract] OR ESRD[Title/Abstract] OR "end stage renal failure"[Title/Abstract] OR ESRF[Title/Abstract) OR "chronic kidney disease"[Title] OR CKD[Title] OR "chronic kidney failure"[Title] OR CKF[Title])	31,004

No.	Query	Hits*
2	(dialysis[MeSH Terms] OR renal dialysis[MeSH Terms] OR hemofiltration[MeSH Terms] OR dialysis[Title/Abstract] OR "renal dialysis"[Title/Abstract] OR haemodialysis[Title/Abstract] OR hemodialysis[Title/Abstract] OR "peritoneal dialysis"[Title/Abstract] OR haemofiltration[Title/Abstract] OR hemofiltration[Title/Abstract] OR haemodiafiltration[Title/Abstract] OR hemodiafiltration[Title/Abstract])	34,639
3	1 AND 2	12,892
4	("Adverse event"[Title/Abstract] OR "adverse events"[Title/Abstract] OR "adverse reaction"[Title/Abstract] OR "adverse reactions"[Title/Abstract] OR safety[Title/Abstract] OR complication[Title/Abstract] OR infection OR sepsis OR peritonitis OR (Malfunctioning AND catheter) OR stenosis)	1,202,309
5	(Meta-analysis[Publication Type] OR systematic review[Publication Type])	136,179
6	4 AND 5	39,726
7	3 AND 6	223
8	(abstracts[Publication Type] OR case reports[Publication Type] OR clinical conference[Publication Type] OR congresses[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, NIH"[Publication Type] OR guideline[Publication Type] OR "meeting abstracts"[Publication Type] OR "practice guideline"[Publication Type] OR review[Publication Type] OR editorial[Publication Type] OR letter[Publication Type] OR comment[Publication Type])	1,417,804
9	(child[Title] OR children[Title] OR pediatric[Title] OR adolescent[Title] OR neonatal[Title])	223,032
10	(Covid-19[Title] OR COVID[Title] OR SARS-Cov2[Title])	177,703
11	8 OR 9 OR 10	1,712,098
12	7 NOT 11	180

*Limited to English and from 2017 to now.

Table 86: CENTRAL search strategy

No.	Query	Hits*
1	MeSH descriptor: [Kidney Failure, Chronic]	4,888
2	("chronic renal failure" OR chronic renal insufficiency" OR end stage kidney disease" OR ESKD OR "end stage renal disease" OR ESRD OR "end stage renal failure" OR ESRF OR "chronic kidney disease" OR CKD OR "chronic kidney failure" OR CKF):ti,ab,kw	61
3	1 OR 2	61

No.	Query	Hits*
4	(dialysis OR "renal dialysis" OR haemodialysis OR hemodialysis OR "peritoneal dialysis" OR haemofiltration OR hemofiltration OR haemodiafiltration OR hemodiafiltration):ti,ab,kw	59
5	MeSH descriptor: [Dialysis]	236
6	MeSH descriptor: [Renal Dialysis]	5,570
7	MeSH descriptor: [Hemofiltration]	624
8	4 OR 5 OR 6 OR 7	59
9	3 AND 8	34
10	("Adverse event" OR "adverse events" OR "adverse reaction" OR safety OR complication OR infection OR sepsis OR peritonitis OR (Malfunctioning AND catheter) OR stenosis)):ti,ab,kw	2,456
11	9 AND 10)	30
12	(Meta-analysis OR systematic review):ti,ab,kw	1,684
13	11 AND 12	20
14	(children OR pediatric OR adolescent OR neonatal OR COVID-19 OR COVID OR SARS-Cov2):ti,ab,kw	1157
15	13 NOT 14	3

ti: title, i.e. free text terms appearing in titles of articles; ab: abstract, i.e. free-text terms appearing in abstracts of articles; kw: keywords, i.e. free-text terms appearing in abstracts of articles
*Limited to English and 2017-current

Systematic selection of studies

The systematic selection of studies in the literature search on safety data on dialysis treatment followed the PICO framework and is specified in Table 87. The criteria were developed to support the overall objective of the systematic literature search. Generally, we included studies in which adults with CKD were treated with long-term dialysis. We included studies that reported AE or complication rates. The inclusion criteria were designed to capture rates for HD and PD, respectively. Furthermore, we only included full-text publications.

Table 87: Inclusion and exclusion criteria in the literature search

	Inclusion	Exclusion
Population	Adult people with CKD	Children and patients with other diseases Comorbidities (if the primary interest in the publication)

Intervention/ comparators	Long-term dialysis (haemodialysis or peritoneal dialysis, haemodiafiltration)	Not long-term dialysis or other treatment options in patients on dialysis
Outcomes	The proportion of patients with adverse effects or complications associated with HD and PD, respectively	Adverse events with no rates. Other outcomes
Study/publication types	Systematic reviews or meta-analysis	Other
Language	English	Other languages
Timeframe	Last five years	Published prior to 2017

The results of the literature search and the flow of studies through the review, including the applied exclusion reasons, are presented in Figure 21.

We identified 3 records in CENTRAL and 180 records in Medline. In total, 180 records were identified after removal of duplicates. Of these, 147 records were excluded based on title/abstract screening, and an additional #22 records were excluded based on review at the full-text level, leaving 11 relevant studies for inclusion in the assessment.

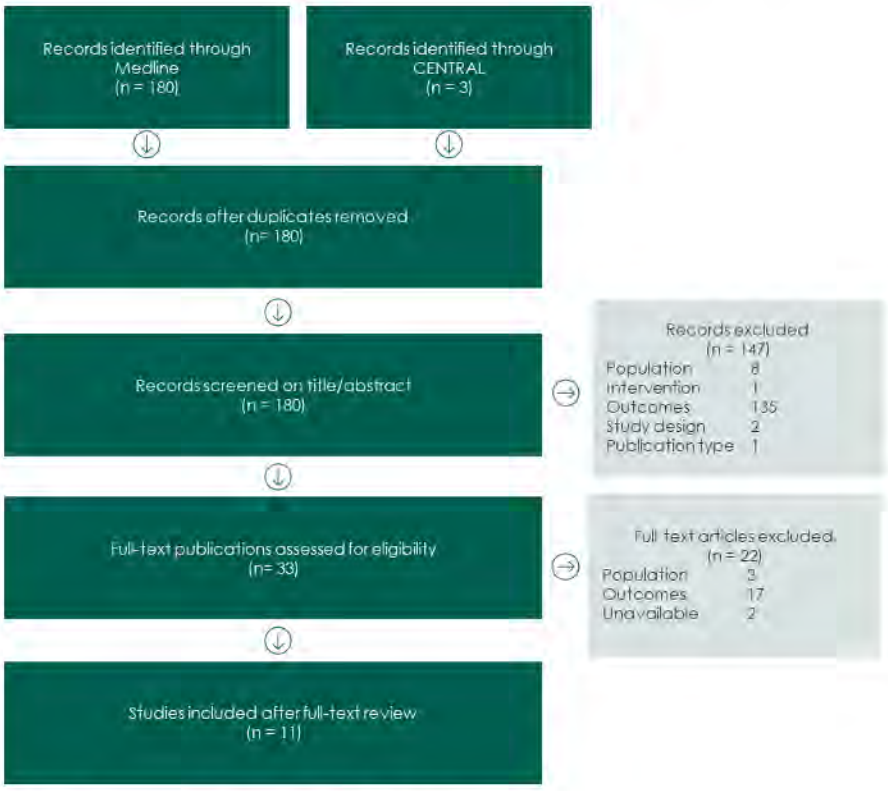


Figure 21: PRISMA flow diagram of the dialysis search

Table 88 lists the 22 articles that were excluded after the full-text assessment, including an explanation as to why each article was excluded.

Table 88: Publications excluded at full-text level

Author(s)	Year	Title	Reason for exclusion
Viecelli et al. **(85)**	2017	Vascular Access Outcomes Reported in Maintenance Hemodialysis Trials: A Systematic Review	Wrong outcome. The review investigates the percentage of trials reporting different vascular access outcomes. It does not provide a proportion of patients with these outcomes.
Htay et al. **(86)**	2021	Urgent-start peritoneal dialysis versus haemodialysis for people with chronic kidney disease	Wrong population. The study includes both adults and children with CKD.
Htay et al. **(87)**	2020	Urgent-start peritoneal dialysis versus conventional-start peritoneal dialysis for people with chronic kidney disease	Wrong population. The study includes both adults and children with CKD.
Zhong et al. **(88)**	2018	The role of hypoxia-inducible factor stabilizers in the treatment of anemia in patients with chronic kidney disease	Wrong outcome. The meta-analysis investigates the effects of HIF stabilisers on anaemia in CKD patients. It does not report adverse events associated with dialysis.
Ali et al. **(89)**	2021	The effects of dialysis modality choice on cognitive functions in patients with end-stage renal failure: a systematic review and meta-analysis	Wrong outcome. Cognitive dysfunction is not categorised as an adverse event.
Tian et al. **(90)**	2019	The comparison of cognitive function and risk of dementia in CKD patients under peritoneal dialysis and hemodialysis	Wrong outcome. Cognitive dysfunction and dementia are not categorised as adverse events.
Wu et al. **(91)**	2021	Systematic review and meta-analysis: the effect and safety of peritoneal dialysis in patients with end-stage diabetic kidney disease	Wrong population. The population has diabetes as a comorbidity.
Boonpheng et al. **(92)**	2019	Risk of hip fracture in patients on hemodialysis versus peritoneal dialysis: A meta-analysis of observational studies	Wrong outcome. The meta-analysis only reports a risk estimate and does not provide a proportion of patients with adverse events.
Ling et al. **(93)**	2019	A systematic review and meta-analysis of the comparison of performance among step-tip, split-tip, and symmetrical-tip hemodialysis catheters	Wrong outcome. The study does not investigate adverse events.
Marshall, M. **(94)**	2022	A systematic review of peritoneal dialysis-related peritonitis rates over time from national or regional population-based registries and databases	Wrong outcome. The study presents peritonitis rates and does not provide a proportion of patients with the adverse event.
He et al. **(95)**	2021	A Meta-analysis on the Relationship between Different Dialysis Modalities and Depression in End-stage Renal Disease Patients.	Unavailable. It was not possible to gain access to the review.

Author(s)	Year	Title	Reason for exclusion
Labaki et al. **(96)**	2020	Anti-neoplastic agents for patients on peritoneal dialysis: A systematic review.	Wrong outcome. The article investigates the association between the dose of anti-neoplastic agents and adverse events.
Lu et al. **(97)**	2022	Comparative Analysis of Efficacy and Prognosis of Hemodialysis and Peritoneal Dialysis for End-Stage Renal Disease: A Meta-analysis.	Wrong outcome. The study does not report proportions of patients with adverse events but compares incidence rates between two groups.
Ng et al. **(98)**	2021	Comparison of cardiovascular mortality in hemodialysis versus peritoneal dialysis.	Wrong outcome. Cardiovascular mortality is not categorised as an adverse event.
Lozier et al. **(99)**	2019	Comparison of Cardiovascular Outcomes by Dialysis Modality: A Systematic Review and Meta-Analysis.	Wrong outcome. The study does not report proportions of patients with adverse events.
Ding et al. **(100)**	2022	Comparison of mortality and complications between urgent-start peritoneal dialysis and urgent-start hemodialysis: A systematic review and meta-analysis.	Wrong outcome. The study reports a risk estimate and does not provide a proportion of patients with adverse events.
Zhan et al. **(101)**	2019	Comparison of risk of stroke in patients treated with peritoneal dialysis and hemodialysis: a systematic review and meta-analysis	Wrong outcomes. The review does not investigate adverse events associated with dialysis.
Tsujimoto et al. **(102)**	2019	Dialysate temperature reduction for intradialytic hypotension for people with chronic kidney disease requiring haemodialysis	Wrong outcome. The study investigates the effects of dialysate temperature reduction on IDH. It does not report any adverse events associated with dialysis.
Sahlawi et al. **(103)**	2020	Peritoneal dialysis-associated peritonitis outcomes reported in trials and observational studies: A systematic review.	Wrong outcome. The article does not report proportions of different adverse events.
Shea et al. **(104)**	2019	Prevalence of cognitive impairment among peritoneal dialysis patients: a systematic review and meta-analysis.	Wrong outcome. Cognitive impairment is not categorised as an adverse event associated with dialysis.
Pyrigdis et al. **(105)**	2021	Prevalence of Erectile Dysfunction in Patients With End-Stage Renal Disease: A Systematic Review and Meta-Analysis	Unavailable. It was not possible to gain access to the review.
Abbasi et al. **(106)**	2020	Risk factors associated with nosocomial infections among end stage renal disease patients undergoing hemodialysis: A systematic review.	Wrong outcome. The study does not report a proportion of patients with adverse events.

The full-text assessment identified 11 eligible studies. These studies were subsequently assessed based on four criteria: The size of the sample, the relevance of the patient population, whether the aim of the study was to investigate adverse events associated to dialysis, and the number of relevant adverse events. The assessment of each study was based on

a combination of these four criteria. Swai et al. was the study that fulfilled the criteria to the highest extent. Table 89 shows the 10 articles that were excluded based on the second assessment's criteria.

Table 89 Reason for exclusion at second assessment

Author(s)	Year	Title
Huang et al. **(107)**	2022	Comparison of Outcomes between Percutaneous and Surgical Placement of Peritoneal Dialysis Catheters in Uremic Patients: A Meta-Analysis
Jiang & Zheng **(108)**	2022	Outcomes of peritoneal dialysis in elderly vs non-elderly patients: A systemic review and meta-analysis
Kuipers et al. **(109)**	2019	The Prevalence of Intradialytic Hypotension in Patients on Conventional Hemodialysis: A Systematic Review with Meta-Analysis
Li et al. **(110)**	2019	Prevalence of pulmonary hypertension in peritoneal dialysis patients: A meta-analysis
Meng et al. **(111)**	2021	Comparison of outcomes of peritoneal dialysis between patients after failed kidney transplant and transplant-naïve patients: a meta-analysis of observational studies
Tavakoli et al. **(112)**	2020	Seroepidemiology of Hepatitis E Virus Infection in Patients Undergoing Maintenance Hemodialysis: A Systematic Review and Meta-Analysis
Xievi et al. **(113)**	2021	Urgent-start peritoneal dialysis in chronic kidney disease patients: A systematic review and meta-analysis compared with planned peritoneal dialysis and with urgent-start hemodialysis
Yin et al. **(114)**	2022	Outcome and Safety of Unplanned-Start Peritoneal Dialysis according to Break-In Periods: A Systematic Review and Meta-Analysis
Zhang et al. **(115)**	2018	Is Peritoneal Dialysis a Suitable Renal Replacement Therapy Option for Polycystic Kidney Disease Patients?
Zuvela et al. **(116)**	2018	Gastrointestinal symptoms in patients receiving dialysis: A systematic review

The systematic literature search identified one# relevant publication. Table 90 provides an overview of the study including aim, study design, patient population intervention and outcomes. Data on adverse events from Swai et al. 2012 (,77) will be included in the health economic model.

Table 90: Overview of study included in the assessment of dialysis AEs

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period
Systematic review and meta-analysis of clinical outcomes comparison between different initial dialysis modalities in end-stage renal disease patients due to lupus nephritis prior to renal transplantation	The aim was to compare the risk of lupus flares, all-cause infections, all-cause cardiovascular events and mortality between haemodialysis versus peritoneal dialysis as initial RRT – modality before renal transplant in LN-ESRD patients	Systematic review and meta-analysis	End-stage renal disease patients due to lupus nephritis prior to renal transplantation	Haemodialysis and peritoneal dialysis All-cause infections: N = 1321 All-cause cardiovascular events: N = 1639	All-cause infections and all-cause cardiovascular events No follow-up period

Survival and quality of life of dialysis

We conducted a systematic literature review to identify relevant survival and HRQoL data on patients with ESRD on dialysis. This appendix describes how the literature search used to identify HRQoL evidence was performed. Below, we list the objective of the literature search and describe the applied data sources, search string etc. Then, we specify the inclusion and exclusion criteria for the search, followed by a description of the systematic selection of studies and reasons for the exclusion of full-text articles. Finally, we describe the strengths and weaknesses of the performed literature search and address the quality of unpublished data.

Objective of the literature search

The objective of the literature search was to identify survival and HRQoL data associated with the two types of dialysis, HD and PD.

Data sources

We searched for relevant literature in the databases Medline (via the PubMed platform) and CENTRAL (via the Cochrane platform) on 8 July 2022 (Table 91). Moreover, we searched the International HTA database for records on dialysis (Table 92). We did not search specifically for any conference material. We searched for records in the

International HTA database by searching for dialysis and CKD. Records were excluded if they were from before 2012. The search of the International HTA database was completed on 28 April 2022.

Table 91: Bibliographic databases included in the literature search for HRQoL data

Database	Platform	Relevant period for the search	Date of search completion
CENTRAL	Cochrane	From 2017 and until today	08.07.2022
Medline	PubMed	From 2017 and until today	08.07.2022

Table 92: Database included in the search

Database	Platform	Search strategy	Date of search
International HTA database	https://database.inahta.org/	We searched for records, including dialysis and chronic kidney disease We followed the PICO criteria (Table 87) and excluded records if they were from before 2012, did not include patients on dialysis and did not include any of the relevant outcomes (survival)	28.04.2022

The search in the International HTA database resulted in the identification of six records after excluding records from before 2012. Based on an initial screening of abstract/summary, four records were excluded because they did not include the relevant population. The remaining two records did not include any relevant outcomes. Thus, the search of the International HTA database did not identify any records relevant to this application.

Search strategy

The search strings used to identify relevant publications presenting survival or HRQoL data for ESRD patients combined MESH terms and free-search terms representing the diagnosis ESRD, the comparator (dialysis) and survival and HRQoL. The syntax, the included search terms and the retrieved hits are presented in Table 93 and Table 94 for Medline and CENTRAL, respectively.

The search strategy included publications from the last five years and meta-analysis or systematic literature reviews, as we wished to identify recent high-quality studies with many observations. The strategy initially focused on these studies but would be extended if no relevant studies were identified within this step of the search.

Table 93: Search terms used in the Medline search

#	Search string	Hits*

1	(end stage kidney disease[MeSH Terms] OR end stage renal disease[MeSH Terms] OR end stage renal failure[MeSH Terms] OR "chronic renal failure"[Title] OR "chronic renal insufficiency"[Title] OR "end stage kidney disease"[Title/Abstract] OR ESKD[Title/Abstract] OR "end stage renal disease"[Title/Abstract] OR ESRD[Title/Abstract] OR "end stage renal failure"[Title/Abstract] OR ESRF[Title/Abstract] OR "chronic kidney disease"[Title] OR CKD[Title] OR "chronic kidney failure"[Title] OR CKF[Title])	31,004
2	(dialysis[MeSH Terms] OR renal dialysis[MeSH Terms] OR hemofiltration[MeSH Terms] OR dialysis[Title/Abstract] OR "renal dialysis"[Title/Abstract] OR haemodialysis[Title/Abstract] OR hemodialysis[Title/Abstract] OR "peritoneal dialysis"[Title/Abstract] OR haemofiltration[Title/Abstract] OR hemofiltration[Title/Abstract] OR haemodiafiltration[Title/Abstract] OR hemodiafiltration[Title/Abstract])	34,639
3	1 AND 2	12,892
4	(mortality[Subheading] OR "Mortality/statistics and numerical data"[Mesh] OR "Mortality/epidemiology"[Mesh] OR "Survival/statistics and numerical data"[Mesh] OR "long term survival"[Title/Abstract] OR "long-term survival"[Title/Abstract] OR mortality risk[Title/Abstract] OR relative mortality[Title/Abstract] OR mortality ratio[Title/Abstract] OR mortality rate[Title/Abstract] OR survival rate[Title/Abstract] OR survival ratio[Title/Abstract] OR relative survival[Title/Abstract])	181,497
5	(utilit*[Title/Abstract] OR disutilit*[Title/Abstract] OR quality of life[MeSH Terms] OR "Quality of life"[Title/Abstract] OR QoL[Title/Abstract] OR HRQoL[Title/Abstract] OR EuroQol[Title/Abstract] OR "EuroQoL 5 Domain"[Title/Abstract] OR EQ-5D[Title/Abstract] OR EQ5D[Title/Abstract] OR "Short-form 36 Health Survey"[Title/Abstract] OR SF-36[Title/Abstract] OR SF36[Title/Abstract] OR KDQOL[Title/Abstract] OR "Kidney Disease Quality of Life"[Title/Abstract])	223,402
6	3 AND (4 OR 5)	3,243
7	(Meta-analysis[Publication Type] OR systematic review[Publication Type])	136,179
8	6 AND 7	195
9	(abstracts[Publication Type] OR case reports[Publication Type] OR clinical conference[Publication Type] OR congresses[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, NIH"[Publication Type] OR guideline[Publication Type] OR "meeting abstracts"[Publication Type] OR "practice guideline"[Publication Type] OR review[Publication Type] OR editorial[Publication Type] OR letter[Publication Type] OR comment[Publication Type])	1,417,804
10	(child[Title] OR children[Title] OR pediatric[Title] OR adolescent[Title] OR neonatal[Title])	223,032
11	(Covid-19[Title] OR COVID[Title] OR SARS-Cov2[Title])	177,703
12	9 OR 10 OR 11	1,712,098
13	8 NOT 12	152

* Limited to English and 2017-current.

Table 94: Search terms used in the CENTRAL search

#	Search string	Hits*

1	MeSH descriptor: [Kidney Failure, Chronic]	4,888
2	("chronic renal failure" OR chronic renal insufficiency" OR end stage kidney disease" OR ESKD OR "end stage renal disease" OR ESRD OR "end stage renal failure" OR ESRF OR "chronic kidney disease" OR CKD OR "chronic kidney failure" OR CKF):ti,ab,kw	61
3	1 OR 2	61
4	(dialysis OR "renal dialysis" OR haemodialysis OR hemodialysis OR "peritoneal dialysis" OR haemofiltration OR hemofiltration OR haemodiafiltration OR hemodiafiltration):ti,ab,kw	59
5	MeSH descriptor: [Dialysis]	5,570
6	MeSH descriptor: [Renal Dialysis]	
7	MeSH descriptor: [Hemofiltration]	624
8	4 OR 5 OR 6 OR 7	59
9	3 AND 8	34
10	(mortality OR "long term survival" OR "long-term survival" OR mortality risk OR relative mortality OR mortality ratio OR mortality rate OR survival rate OR survival ratio OR relative survival):ti,ab,kw	1,169
11	MeSH descriptor: [Mortality]	14,085
12	MeSH descriptor: [Survival]	134
13	10 OR 11 OR 12	959
14	(utilit* OR disutilit* OR "Quality of life" OR QoL OR HRQoL OR EuroQol OR "EuroQoL 5 Domain" OR EQ-5D OR EQ5D OR "Short-form 36 Health Survey" OR SF-36 OR SF36 OR KDQOL OR "Kidney Disease Quality of Life"):ti,ab,kw	1,240
15	MeSH descriptor: [Quality of Life]	29,134
16	14 OR 1	1,240
17	13 OR 16	1,764
18	9 AND 17	28
19	(Meta-analysis OR systematic review):ti,ab,kw	1,684
20	18 AND 19	20
21	(child OR children OR pediatric OR adolescent OR neonatal OR COVID-19 OR COVID OR SARS-Cov2):ti,ab,kw	960
22	20 NOT 21	14

ti: title, i.e. free text terms appearing in titles of articles; ab: abstract, i.e. free-text terms appearing in abstracts of articles; kw: keywords, i.e. free-text terms appearing in abstracts of articles
* Limited to English and from 2017 to now.

Systematic selection of studies

The systematic selection of studies in the systematic literature search for survival and HRQoL data followed the PICO framework and is detailed in Table 95. The criteria were developed to support the overall objective of the systematic literature search. The inclusion criteria were: systematic literature reviews on survival or QoL in adult patients with CKD on long-term dialysis.

Table 95: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion
Population	Adult people with CKD	Children and patients with other diseases Comorbidities (if the primary interest in the publication)
Intervention/ comparators	Long-term dialysis (haemodialysis or peritoneal dialysis, haemodiafiltration)	Not long-term dialysis or other treatment options
Outcomes	Survival of dialysis patients on a waiting list for a renal transplant	Survival curves without IPD. Risk factors
	Utility values (preferable EQ-5D) for PD or HD patients. Studies have to include utility values for kidney transplant in addition to dialysis	Utilities that are presented only for health states that are not relevant in the model
Study type	Systematic reviews or meta-analysis	Other
Language	English	Other languages
Geographical	Europe	Rest of the world
Time frame	Last five years	Published prior to 2017

The results of the literature search and the flow of studies through the review rounds are presented in Figure 22 In the literature search, we identified 166 publications. After removing duplicate entries, a total of 158 publications were reviewed. Of these, 145 were excluded on initial review of title and abstract, and nine were excluded at full-text review, leaving one eligible publication with survival data and three eligible publications with relevant HRQoL data.

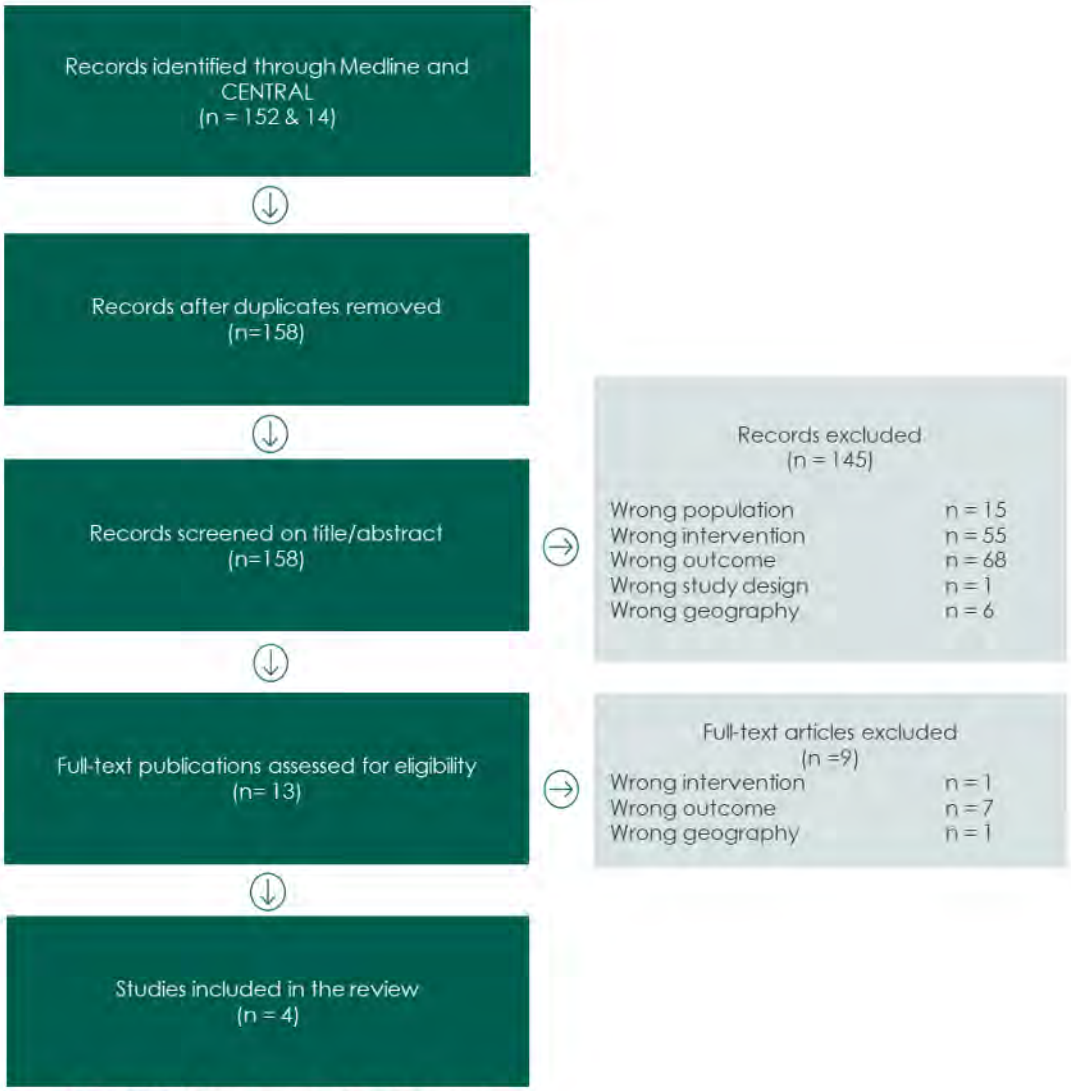


Figure 22: PRISMA flow diagram of HRQoL search

In Table 96, the records excluded at full-text level have been listed with their respective exclusion reasons.

Table 96: Publications excluded at full-text level

Author(s)	Year	Title	Reason for exclusion
Zhao et al.	2018	Timing of Dialysis Initiation and Mortality Risk in Chronic Kidney Disease: A Meta-Analysis	Wrong outcome. The meta-analysis compares the mortality associated with early v. late initiation of dialysis.

Author(s)	Year	Title	Reason for exclusion
Ren et al.	2019	Quality of life, symptoms, and sleep quality of elderly with end-stage renal disease receiving conservative management: a systematic review	Wrong intervention. The study examines the quality of life in chronic kidney patients undergoing conservative disease management, i.e. quality of life and symptom control without dialysis or kidney transplant.
Meng et al.	2021	Comparison of outcomes of peritoneal dialysis between patients after failed kidney transplant and transplant-naïve patients: a meta-analysis of observational studies	Wrong outcome. The meta-analysis investigated the influence of prior failed kidney transplants by comparing peritoneal dialysis outcomes in patients with a failed transplant vs transplant-naïve patients.
Chuasuwan et al.	2020	Comparisons of quality of life between patients underwent peritoneal dialysis and hemodialysis: a systematic review and meta-analysis	Wrong outcome. The study only includes utilities for HD and PD but not kidney transplantation.
Maki et al.	2022	Left ventricular mass regression, all-cause and cardiovascular mortality in chronic kidney disease: a meta-analysis	Wrong outcome. The article does not specify that dialysis patients were on a waiting list for a kidney transplant.
Ju et al.	2019	Patient-reported outcome measures for life participation in kidney transplantation: A systematic review	Wrong outcome. The article discusses different quality-of-life measures but does not provide any utility values.
Jiang and Zheng	2022	Outcomes of peritoneal dialysis in elderly vs non-elderly patients: A systemic review and meta-analysis	Wrong outcome. The article does not specify that dialysis patients were on a waiting list for a kidney transplant.
Elsayed et al.	2020	Propensity score matched mortality comparisons of peritoneal and in-centre haemodialysis: systematic review and meta-analysis	Wrong outcome. The article does not specify that dialysis patients were on a waiting list for a kidney transplant.
Fletcher et al.	2022	Symptom burden and health-related quality of life in chronic kidney disease: A global systematic review and meta-analysis	Wrong geography. The study presents a global pooled analysis of EQ-5D estimates but does not include estimates based solely on European countries.

In the systematic literature review, we identified four eligible publications, one presenting survival data and three presenting utilities for the relevant health states. . The eligible systematic literature review on survival in patients on

dialysis (3) and the three systematic literature reviews presenting data on HRQoL of dialysis patients (118–120) are summarised in Table 97 and Table 98, respectively.

The study by Chaudhry et al. 2022 is a systematic literature review and meta-analysis investigating the survival benefit of transplantation vs dialysis for waitlisted kidney failure patients. The study presents a pooled HR for survival including European studies (3). Among others, the pooled analysis include a publication by Sørensen et al. 2016 which presents Danish survival estimates for patients on dialysis compared to patients on a waiting list (41). Due to the larger study population and the validity of meta-analyses, Chaudhry et al. 2022 (3) has been applied in the base case of the health economic model, while estimates from Sørensen et al. 2016 (41) have been tried in a sensitivity analysis.

The three studies that included HRQoL data, Yang et al. 2021 (119), Cooper et al. 2020 (118) and Elshahat et al. 2020 (120), were systematic literature reviews. The study by Cooper et al. (118) presented results from a pooled global meta-analysis. However, as the PICO criteria require eligible data to be European, the pooled estimates were not considered in this application. Instead, HRQoL estimates from relevant publications (based on the PICO criteria), identified in the three respective systematic literature reviews, have been considered for the application. The UK study by Lee et al. 2005 (56) was identified in both Cooper et al. 2020 (118) and Yang et al. 2021 (119), and from the Elshahat et al. 2020 (120) study, we identified the Eriksson et al. 2017 (67) study, which reports HRQoL for Nordic CKD patients. In the health economic model, Lee et al. 2005 (56) was applied in the base case, and Eriksson et al. 2017 (67) was applied in a sensitivity analysis. Although the search strategy was defined to identify HRQoL data for dialysis patients, the two eligible studies also included HRQoL data for patients with a functioning graft following transplant. Therefore, we did not perform any further literature search for HRQoL data but included these studies for all health states in the model.

Table 97: Summary of eligible studies on survival

Study	**Chaudry et al. 2022** (3) **European pooled analysis**	**Sørensen et al. 2016** (41)
Population	Patients who have undergone renal transplantation versus patients who are on dialysis and are on a waiting list for a transplant	Patients who have undergone renal transplantation versus patients who are on dialysis and are on a waiting list for a transplant
Intervention	Renal transplantation	Renal transplantation
Comparators	Dialysis	Dialysis
Sample size	34,467	1,639
Country	Multiple countries in Europe	Denmark
Method of analysis	HR of mortality for transplantation vs dialysis	HR of mortality for transplantation vs dialysis
Survival (HR)	0.49	0.38

Table 98: Summary of studies on HRQoL

Study	**Lee et al. 2005** (56)	**Eriksson et al. 2017** (67)

Population	Renal failure	Autosomal dominant polycystic kidney disease
Country	UK	The Nordics
Sample size	416	Dialysis: 61 Transplantation: 63
Description of health states	Kidney transplant with functioning graft, PD, HD and pre-dialysis (waiting initiation of dialysis)	Maintenance dialysis and kidney transplant
Method of evaluation	EQ-5D	EQ-5D

Quality assessment and generalisability of estimates

During the screening and review of studies, the relevance of any identified utilities and the quality of the studies generating them was assessed. This process enables justification of the use/non-use of different input values in the economic model.

The performed literature searches have a number of strengths and weaknesses. For imlifidase data, we conducted a systematic literature search applying the two databases Medline and Embase, and for the dialysis input, we conducted systematic literature reviews applying the two databases Medline and CENTRAL as requested by the Danish Medicines Council. The PICO and the inclusion and exclusion criteria were defined before the literature searches. We applied relevant search terms for the intervention, comparators and outcomes of interest.

A weakness of the performed literature searches is that only one researcher screened the records on title/abstract and later conducted the full-text assessment. However, if the researcher was in doubt about a specific article, this was always discussed with the project manager before deciding to include or exclude the article.

Unpublished data

Unpublished data were not included in the health economic model.

Appendix B – Main characteristics of included studies

In the following, we present the main characteristics of the trials included in the application.

Table 99: Main characteristics of 17-HMedIdeS-14 (Study 14). Source: Hansa data on file.

Trial name: A prospective, observational long-term follow-up study of patients treated with imlifidase (IdeS) prior to kidney transplantation (17-HMedIdeS-14)	**NCT number: NCT03611621**
Objective	The purpose of this study is to collect data from extended follow-up in subjects that have received a kidney transplant following imlifidase dosing to provide a better understanding of the long-term outcome for these subjects.
Publications – title, author, journal, year	A publication with three-year data from Study 14 is available. The publication is based on a subset of patients from Study 14 (only patients with three-year data available): Kjellman et al.: Outcomes at 3 years posttransplant in imlifidase-desensitized kidney transplant patients, American Journal of Transplantation, 2021 July, volume 21, issue 12 pages 3907-3918 (40).
Study type and design	A phase 2, prospective, observational, long-term (five-year), follow-up study. The study will primarily determine the time of graft survival in subjects who have received imlifidase prior to kidney transplantation in the feeder studies: 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS- 04 and 15-HMedIdeS-06. The subjects attend four follow up visits 1, 2, 3 and 5 years after imlifidase administration.
Sample size (n)	n=35 Patient enrolled from studies: 13-HMedIdeS-02: n=1 13-HMedIdeS-03: n=10 14-HMedIdeS- 04: n=11 15-HMedIdeS-06: n= 13
Main inclusion and exclusion criteria	Eligible subjects met all the following inclusion criteria (from www.clinicaltrials.gov): • Persons above the age of 18 • Subjects that have participated, or are currently participating, in the imlifidase kidney transplantation studies: 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06 Reasons for exclusion were (from www.clinicaltrials.gov): • Deemed unable to comply with the protocol • Inability, by the judgement of the investigator, to participate in the study for other reasons
Intervention	No active intervention was included, as the purpose of the study was to collect data on patients who have received a kidney transplant following imlifidase.
Comparator(s)	None
Follow-up time	The total follow-up time for the study was five years.

Trial name: A prospective, observational long-term follow-up study of patients treated with imlifidase (IdeS) prior to kidney transplantation (17-HMedIdeS-14)	NCT number: NCT03611621

Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

Primary endpoint:

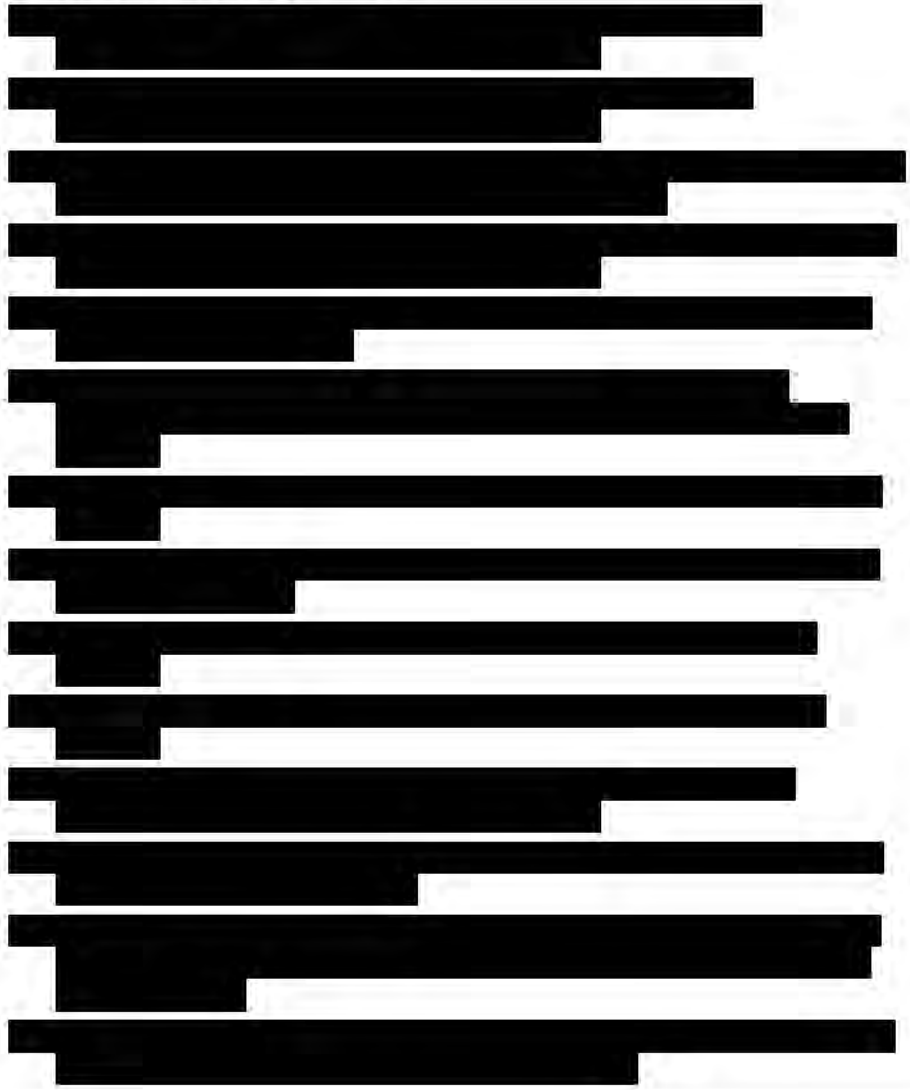
The primary endpoint of this study is to determine overall graft survival, defined as time from transplantation to graft loss at 1, 2, 3 and 5 years after first dose of imlifidase. Graft loss is defined as permanent return to dialysis for at least six weeks, re-transplantation, or transplantectomy. If dialysis was used to define graft loss, the date of graft loss was the first day of the last ongoing dialysis period reported.

Time frame: five years after first dose of imlifidase.

Secondary endpoints:

The secondary endpoints of this study were:

- Overall graft survival (not censored for death). This endpoint was not evaluated in the first status report (data cut-off 2019) for this study because at that time there was not sufficient data available to support this analysis.
- Overall patient survival defined as time from transplantation to death for any cause. Time frame: five years after first dose of imlifidase
- Evaluation of long-term kidney function assessed by eGFR. Time frame: five years after first dose of imlifidase



Trial name: A prospective, observational long-term follow-up study of patients treated with imlifidase (IdeS) prior to kidney transplantation (17-HMedIdeS-14)	NCT number: NCT03611621
	• Evaluation of health-related quality of life with patient questionnaires KDQOL-SF. Time frame: five years after first dose of imlifidase
Method of analysis	The FAS was defined as all patients enrolled. It should be noted that the FAS not only consisted of patients who have given their own consent to participate but also, after permission from concerned IECs/IRBs, patients who died after the end of the feeder study but prior to being enrolled in the current study. The FAS also includes patients who have experienced graft loss after the end of the feeder study but prior to being enrolled in the study. Because of the non-interventional nature of this study, no other analysis set was defined, and all data presentations and analyses are based on the FAS. The primary endpoint is analysed by the Kaplan-Meier survival method. The overall graft survival is tabulated and presented graphically with 95% confidence limits. The primary analysis is based on intervals of one year. The following events were censored at the time of occurrence: withdrawal from the study without graft loss, death not caused by graft loss, evaluation time point (the yearly evaluations) and end of study without graft loss. The Kaplan-Meier analysis is not comparative in this study because of the non-interventional nature of the study. Hence, there is no formal statistical hypothesis or testing. The secondary endpoint, patient survival, was analysed in the same way as the primary endpoint, and the following events were censored: withdrawal from the study, evaluation time point (the yearly evaluations) and end of study. As this was a non-interventional follow-up study, no power calculations for sample size estimation were performed.
Subgroup analyses	None
Other relevant information	None

Table 100: Main characteristics of 13-HMedIdeS-02 (Study 02). Source: Hansa data on file.

Trial name: Study 02: A Phase II Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous IdeS After Administration of Ascending Doses in Chronic Kidney Disease Patients (13-HMedIdeS-02)	NCT number: NCT02224820
Objective	The primary objective was to find an IdeS dosing scheme which resulted in HLA antibody levels which were acceptable for transplantation in the majority of the patients. [redacted]

Trial name: Study 02: A Phase II Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous IdeS After Administration of Ascending Doses in Chronic Kidney Disease Patients (13-HMedIdeS-02)	NCT number: NCT02224820
Publications – title, author, journal, year	The following two scientific publications are indexed to this study (on clinicaltrials.gov): • Lorant T, Bengtsson M, Eich T, Eriksson BM, Winstedt L, Järnum S, Stenberg Y, Robertson AK, Mosén K, Björck L, Bäckman L, Larsson E, Wood K, Tufveson G, Kjellman C. Safety, immunogenicity, pharmacokinetics, and efficacy of degradation of anti-HLA antibodies by IdeS (imlifidase) in chronic kidney disease patients. Am J Transplant. 2018 Nov;18(11):2752- 62 • Jordan SC, Lorant T, Choi J, Kjellman C, Winstedt L, Bengtsson M, Zhang X, Eich T, Toyoda M, Eriksson BM, Ge S, Peng A, Järnum S, Wood KJ, Lundgren T, Wennberg L, Bäckman L, Larsson E, Villicana R, Kahwaji J, Louie S, Kang A, Haas M, Nast C, Vo A, Tufveson G. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation. N Engl J Med. 2017 Aug 3;377(5):442-53
Study type and design	Phase 2, uncontrolled, non-randomised, single-centre, ascending-dose trial
Sample size (n)	8 patients

Trial name: Study 02: A Phase II Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous IdeS After Administration of Ascending Doses in Chronic Kidney Disease Patients (13-HMedIdeS-02)	NCT number: NCT02224820
Main inclusion and exclusion criteria	Eligible subjects met all the following inclusion criteria: • Above the age of 18 • Diagnosis of chronic kidney disease and in dialysis with identified antibodies against at least two HLA antigens, of which at least one is 3000 MFI or more as measured by SAB assay on at least two occasions Reasons for exclusion were: • Prior malignancy within two years, excluding adequately treated basal cell or squamous cell skin cancer, cervical carcinoma in situ and prostate cancer Gleason <6 and prostate-specific antigen (PSA) <10ng/mL • Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus (HIV) • Clinical signs of ongoing infectious disease • Severe other conditions requiring treatment and close monitoring, e.g., cardiac failure >New York Heart Association (NYHA) grade 3, unstable coronary disease or oxygen-dependent chronic obstructive pulmonary disease (COPD) • History of any other clinically significant disease or disorder which, in the opinion of the investigator, may either put the patient at increased risk because of participation in the study or influence the results or the patient's ability to participate in the study • Hypogammaglobulinemia, defined as any values of P-total IgG less than 3 g/L • History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to IdeS (e.g., streptokinase and/or staphylokinase) • Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within four months of the first administration of investigational product in this study. Patients consented and screened but not dosed in previous studies were not excluded.
Intervention	Imlifidase administered in ascending doses: 0.12 and 0.25 mg/kg once or twice within 48 hours
Comparator(s)	None
Follow-up time	The induction phase of the study was 48 hours, and the total follow-up time for the study was 64 days.
Is the study used in the health economic model?	No

Trial name: Study 02: A Phase II Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous IdeS After Administration of Ascending Doses in Chronic Kidney Disease Patients (13-HMedIdeS-02)	NCT number: NCT02224820
Primary, secondary and exploratory endpoints	**Primary endpoints:** The primary efficacy endpoint was the IdeS dosing scheme in the majority of the patients resulting in HLA antibody levels which are acceptable for transplantation, measured as MFI of less than 1100, within 24 hours from dosing. MFI was determined by single antigen bead (SAB) assay and detection of complement fixating ability (CIq Screen) in serum. **Secondary endpoints:** Secondary endpoints for safety, pharmacodynamics, immunogenicity, and pharmacokinetics were: • Reduction of PRA levels in cytotoxic sera screen after IdeS treatment • Result in FACS crossmatch test against available donor cells after IdeS treatment • Safety parameters (adverse events, clinical laboratory tests, vital signs and ECGs) • Pharmacokinetic (PK) profile of IdeS • Pharmacodynamic (PD) profile of IdeS (cleavage of IgG) • Immunogenicity of IdeS by measuring anti-drug antibodies.
Method of analysis	The safety analysis set includes all randomised patients that received any amount of study medication. All eight patients received study drug and were thus included in the safety set. The FAS consisted of all patients in the safety set that has a measurement of anti-HLA antibody level within 24 hours from dosing.
Subgroup analyses	None
Other relevant information	None

Table 101: Main characteristics of 13-HMED-IdeS-03 (Study 03). Source: Hansa data on file.

Trial name: Study 03: A Phase II Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of Intravenous Ascending Doses of IdeS in Kidney Transplantation (13-HMED-IdeS-03)	NCT number: NCT02475551
Objective	The primary objective of the study was to study the safety and tolerability of IdeS. Safety was assessed from the onset of treatment until six months after dosing. Secondary objectives were to determine the following in CKD patients undergoing transplantation: 1) to find an IdeS dose which resulted in HLA antibody levels acceptable for transplantation in the majority of the patients within 24 hours from dosing, 2) Cytotoxic sera screen, 3) FACS cross-match test, 4) PK and PD profile of IdeS and 5) the immunogenicity profile of IdeS.

Trial name: Study 03: A Phase II Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of Intravenous Ascending Doses of IdeS in Kidney Transplantation (13-HMED-IdeS-03)	NCT number: NCT02475551
Publications – title, author, journal, year	The following scientific publication is indexed to this trial (on clinicaltrials.gov): • Jordan SC, Lorant T, Choi J, Kjellman C, Winstedt L, Bengtsson M, Zhang X, Eich T, Toyoda M, Eriksson BM, Ge S, Peng A, Järnum S, Wood KJ, Lundgren T, Wennberg L, Bäckman L, Larsson E, Villicana R, Kahwaji J, Louie S, Kang A, Haas M, Nast C, Vo A, Tufveson G. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation. N Engl J Med. 2017 Aug 3;377(5):442-53.
Study type and design	Phase 2 uncontrolled, non-randomised, single-group, ascending-dose study in patients with CKD and intended for transplantation, with ≥1 identified HLA antibody with MFI ≥3000 DD, DL
Sample size (n)	10 patients

Trial name: Study 03: A Phase II Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of Intravenous Ascending Doses of IdeS in Kidney Transplantation (13-HMED-IdeS-03)	NCT number: NCT02475551
Main inclusion and exclusion criteria	Eligible subjects met all the following inclusion criteria: • Above the age of 18 • Diagnosed with chronic kidney disease and in dialysis with preformed anti-HLA antibodies (non-DSA, DSA or both), negative T-CDC CXM and at least one antibody MFI >3000. Reasons for exclusion were: • Prior malignancy within two years, excluding adequately treated basal cell or squamous cell skin cancer, cervical carcinoma in situ and prostate cancer Gleason <6 and prostate-specific antigen (PSA) <10ng/mL • Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus (HIV) • Clinical signs of ongoing infectious disease • Severe other conditions requiring treatment and close monitoring, e.g., cardiac failure >New York Heart Association (NYHA) grade 3, unstable coronary disease or oxygen-dependent chronic obstructive pulmonary disease (COPD) • History of any other clinically significant disease or disorder which, in the opinion of the investigator, may either put the patient at increased risk because of participation in the study or influence the results or the patient's ability to participate in the study • Hypogammaglobulinemia, defined as any values of P-total IgG less than 3 g/L • History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to IdeS® (e.g., streptokinase and/or staphylokinase) • Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within four months of the first administration of investigational product in this study. • Patients consented and screened but not dosed in previous studies were not excluded.
Intervention	IdeS as a single infusion: 0.25 and 0.5 mg/kg
Comparator(s)	None
Follow-up time	The total follow-up time for the study was 180 days.
Is the study used in the health economic model?	No

Trial name: Study 03: A Phase II Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of Intravenous Ascending Doses of IdeS in Kidney Transplantation (13-HMED-IdeS-03)	NCT number: NCT02475551
Primary, secondary and exploratory endpoints	**Primary endpoints:** The primary safety endpoint was the adverse events, clinical laboratory tests, vital signs and ECGs within six months. **Secondary endpoints:** • Efficacy, defined as the IdeS dosing scheme resulting in HLA antibody levels acceptable for transplantation within 24 hours from dosing • Reduction of PRA levels in cytotoxic sera screen after IdeS treatment • Result in FACS and cytotoxic crossmatch test after IdeS treatment • PK profile of IdeS • PD profile of IdeS (cleavage of IgG) • Immunogenicity of IdeS by measuring ADA • Time to recovery of total serum IgG and HLA-antibody • Kidney function in patients who were transplanted
Method of analysis	The safety analysis set (SAS) consisted of all patients who received any amount of IMP. The FAS consisted of all patients in the SAS who had a measurement of anti-HLA antibody level within 24 hours of dosing. All efficacy data were presented for the FAS. For individual patients, positive SAB-HLAs (anti-HLA antibodies measured with the SAB assay) and positive SAB-C1qs (anti-HLA antibodies with complement fixation ability measured with the SAB assay) were defined as those having baseline MFI >3000. DSAs were identified as antibodies against the donor HLA type measured in the SAB-HLA assay and in general having an MFI >1100. SAB-HLA, SAB-C1q and DSA data were tabulated by patient and time point and/or as percentage change from baseline by time point, as applicable and as individual and mean profiles of percentage change from baseline. The distribution (MFI) of positive SAB-HLAs/SAB-C1qs was presented as box plots by patient and time point. The DSAs were shown graphically as spaghetti plots of MFI versus time including each DSA for each patient.
Subgroup analyses	None
Other relevant information	None

Table 102: Main characteristics of 14-HMed-IdeS-04 (Study 04). Source: Hansa data on file.

Trial name: Study 04: A Phase I/II Trial to Evaluate the Safety and Tolerability of IdeS® (IgG Endopeptidase) to Eliminate Donor Specific HLA Antibodies (DSAs) and Prevent Antibody-Mediated Rejection Post-Transplant in Highly-HLA Sensitized Patients (14-HMed-IdeS-04)	NCT number: NCT02426684
Objective	The overall objective of this trial was to establish the clinical benefit and investigate the safety and tolerability of infusion of imlifidase at a clinically relevant dose in highly sensitised patients prior to transplantation.
Publications – title, author, journal, year	The following two scientific publications are indexed to this study (on clinicaltrials.gov): • von Pawel-Rammingen U Streptococcal. IdeS and its impact on immune response and inflammation. J Innate Immun. 2012;4(2):132-40 • Jordan SC, Lorant T, Choi J, Kjellman C, Winstedt L, Bengtsson M, Zhang X, Eich T, Toyoda M, Eriksson BM, Ge S, Peng A, Järnum S, Wood KJ, Lundgren T, Wennberg L, Bäckman L, Larsson E, Villicana R, Kahwaji J, Louie S, Kang A, Haas M, Nast C, Vo A, Tufveson G. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation. N Engl J Med. 2017 Aug 3;377(5):442-53
Study type and design	Combined phase 1 and 2, uncontrolled open-label trial
Sample size (n)	17 patients

Main inclusion and exclusion criteria	Eligible subjects met all the following inclusion criteria: • Above the age of 18 • Diagnosed with end-stage renal disease awaiting transplantation on the UNOS list • No known contraindications for therapy with IVIG10%/Rituximab, plasmapheresis (PLEX) or IdeS® • cPRA >50% demonstrated on three consecutive samples, patient highly HLA-sensitised and a candidate for DD transplantation after desensitisation at CSMC • At transplant, patient must have donor-specific antibody/crossmatch-positive (DSA/CMX+) non-HLA-identical donor • Pre-transplant vaccination with Streptococcus pneumoniae and Neisseria meningitides • Subject/Parent/Guardian must be able to understand and provide informed consent. Reasons for exclusion were: • Positivity for anti-IdeS IgE • Use of IVIG four weeks prior to planned IdeS® administration • Recipients of Extended Criteria Donors (ECD) or Living Donors (LD) • Lactating or pregnant females or women of child-bearing age who are not willing or able to practice FDA-approved forms of contraception • HIV-positive subjects • Subjects who test positive for HBV infection [positive HBVsAg, HBVcAb, or HBVeAg/DNA] or HCV infection [positive Anti-HCV (EIA) and confirmatory HCV RIBA] • Subjects with active TB • Subjects with selective IgA deficiency, those who have known anti-IgA antibodies, and those with a history of anaphylaxis or severe systemic responses to any part of the clinical trial material • Subjects who have received or for whom multiple organ transplants are planned • Recent recipients of any licensed or investigational live attenuated vaccine(s) within two months of the screening visit, including but not limited to any of the following: ◦ Adenovirus (Adenovirus vaccine live oral type 7) ◦ Varicella (Varivax) ◦ Hepatitis A (VAQTA) ◦ Rotavirus (Rotashield) ◦ Yellow fever (Y-F-Vax) ◦ Measles and mumps (Measles and mumps virus vaccine live) ◦ Measles, mumps, and rubella vaccine (M-M-R-II) ◦ Sabin oral polio vaccine

	◦ Rabies vaccines (IMOVAX Rabies I.D., RabAvert) ▪ A significantly abnormal general serum screening lab result defined as a WBC <3.0 X 103/ml, a Hgb 8.0 g/dL, a platelet count <100 X 103/ml, an SGOT >3X upper limit ▪ Individuals deemed unable to comply with the protocol ▪ Subjects with active CMV or EBV infection as defined by CMV-specific serology (IgG or IgM) and confirmed by quantitative PCR with or without a compatible illness ▪ Subjects with a known history of previous myocardial infarction within one year of screening ▪ Subjects with a history of clinically significant thrombotic episodes and subjects with active peripheral vascular disease ▪ Subjects with Protein C and Protein S deficiency ▪ Use of investigational agents within four weeks of participation ▪ Known allergy/sensitivity to IdeS® infusions.
Intervention	IdeS 0.24 mg/kg for the first 10 patients. If no PK/PD/safety/tolerability issues were observed, dose was increased to 0.5 mg/kg on day 0 for final 10 patients.
Comparator(s)	None
Follow-up time	The total follow-up time for the study was 180 days.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Primary endpoints:** • Number and levels of DSAs prior to transplantation • Number and levels of DSA levels post-transplantation • Incidence of allograft rejections • Renal function by creatinine, eGFR, and urine protein measurements • Biopsy pathology evaluation • Safety parameters (AEs, laboratory assessments, vital signs, ECG) **Secondary endpoints:** • Incidence of AMR findings at end of study (protocol biopsies) • Incidence of C4d depositions • Long-term allograft function (S-creatinine and eGFR)

Trial name: Study 04: A Phase I/II Trial to Evaluate the Safety and Tolerability of IdeS® (IgG Endopeptidase) to Eliminate Donor Specific HLA Antibodies (DSAs) and Prevent Antibody-Mediated Rejection Post-Transplant in Highly-HLA Sensitized Patients (14-HMed-IdeS-04)	NCT number: NCT02426684
Method of analysis	No formal statistical hypothesis testing was performed in this study. All presentations of data are descriptive by nature. Missing data were in general not imputed or adjusted for in other ways. All patients were administered 0.24 mg/kg, and tabulations do not include any grouping by dose. Numerical data are presented in summary tables by number of patients, arithmetic mean (geometric mean and coefficient of variation (CV) where applicable), median, standard deviation (SD), minimum and maximum. Categorical data are presented by number and percent of patients as well as number of events (where applicable). Endpoints are presented graphically as box plots, mean profile plots, individual profile plots or spaghetti plots. For endpoints where profile and spaghetti plots best represent the data, two separate plots with the time axis including only the initial part or the full duration, respectively, are produced. All data are listed.
Subgroup analyses	None
Other relevant information	None

Table 103: Main characteristics of 15-HMedIdeS-06 (Study 06). Source: Hansa data on file.

Trial name: Study 06: Phase II Study to Evaluate the Efficacy of IdeS (IgG Endopeptidase) to Desensitize Transplant Patients With a Positive Crossmatch Test	NCT number: NCT02790437
Objective	The purpose of this study is to evaluate the effectiveness of the study drug IdeS in creating a negative crossmatch test (XM) in patients who are on the waiting list for a kidney transplant and have previously undergone desensitisation unsuccessfully, or in whom effective desensitisation will be highly unlikely.
Publications – title, author, journal, year	The following scientific publications are indexed to this study: Jordan SC, Legendre C, Desai NM, Lorant T, Bengtsson M, Lonze BE, et al. Imlifidase desensitization in crossmatch-positive, highly-sensitized kidney transplant recipients: Results of an international phase 2 trial (Highdes). Transplantation. 2020.
Study type and design	Phase 2, uncontrolled, multi-centre, open-label single-group trial
Sample size (n)	19 patients

Trial name: Study 06: Phase II Study to Evaluate the Efficacy of IdeS (IgG Endopeptidase) to Desensitize Transplant Patients With a Positive Crossmatch Test	NCT number: NCT02790437

Main inclusion and exclusion criteria	**Eligible subjects met all the following inclusion criteria:** • Between 18 and 70 years old • On the kidney transplant waiting list and have previously undergone desensitisation unsuccessfully, or effective desensitisation is highly unlikely. The breadth and strength of sensitisation will predict an extremely low likelihood of successful desensitisation or kidney paired donation. • Patients with a live or deceased donor with a positive crossmatch test **Reasons for exclusion were:** • Previous treatment with IdeS® • Previous high-dose IVIg treatment (2 g/kg BW) within 28 days prior to IdeS® treatment • Lactating or pregnant females or women of child-bearing age who are not willing or able to practice FDA-approved forms of contraception • HIV-positive patients • Patients with clinical signs of HBV or HCV infection • Patients with active tuberculosis • A significantly abnormal general serum screening lab result according to the investigator's judgement. Hgb cannot be <6.0 g/dL • Severe other conditions requiring treatment and close monitoring, e.g., cardiac failure >NYHA (New York Heart Association) grade 3, unstable coronary disease or oxygen-dependent COPD • Individuals deemed unable to comply with the protocol • Patients with clinical signs of CMV or EBV infection • Patients with a history of major thrombotic events, patients with active peripheral vascular disease or patients with proven hypercoagulable conditions • Patients should not have received investigational drugs within four half-lives (or similar) • Known allergy/sensitivity to IdeS® infusions • Patients who have a live donor and test positive for ImmunoCap anti-IdeS IgE
Intervention	IdeS as a single infusion: 0.25 mg/kg on study day 0. If negative crossmatch was not achieved, a second dose (0.25 mg/kg) was given within two days of the first infusion. Following IdeS treatment, participants underwent kidney transplantation.
Comparator(s)	None
Follow-up time	The total follow-up time for the study was 180 days.

Trial name: Study 06: Phase II Study to Evaluate the Efficacy of IdeS (IgG Endopeptidase) to Desensitize Transplant Patients With a Positive Crossmatch Test	NCT number: NCT02790437
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Primary endpoints:** The primary efficacy endpoint was the number of patients with crossmatch conversion from positive to negative within 24 hours of IdeS® dosing. **Secondary endpoints:** The secondary efficacy endpoints were: ▪ DSA levels at pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180 post-imlifidase treatment ▪ Time to creating a negative CDC CXM test (not applicable in France) ▪ Time to creating a negative FACS CXM test ▪ Safety parameters (AEs, clinical laboratory tests, vital signs and ECGs) ▪ Kidney function after imlifidase treatment assessed by filtration (eGFR), creatinine and proteinuria up to 180 days post-treatment ▪ PK profile of imlifidase up to day 14 ▪ PD profile of imlifidase (cleavage and recovery of IgG) up to day 180 post-imlifidase ▪ Immunogenicity profile of imlifidase by measuring ADA
Method of analysis	No formal statistical hypothesis testing was performed. All presentations of data are descriptive by nature. Missing data were in general not imputed or adjusted for in other ways. Generally, continuous data are presented in summary tables by number of patients, arithmetic mean (geometric mean and CV% where applicable), median, SD, minimum and maximum. Categorical data are presented by number and percentage of patients as well as number of events (where applicable)
Subgroup analyses	None
Other relevant information	None

Table 104: Main characteristics of Chaudhry et al. 2022 study. Source: Chaudhry et al.(3).

Trial name: Survival for waitlisted kidney failure patients receiving transplantation versus remaining on waiting list: systematic review and meta-analysis	Doi: 10.1136/bmj-2021-068769
Objective	Investigate the survival benefit of transplantation versus dialysis for waitlisted kidney failure patients with a priori stratification.

Trial name: Survival for waitlisted kidney failure patients receiving transplantation versus remaining on waiting list: systematic review and meta-analysis	Doi: 10.1136/bmj-2021-068769
Publications – title, author, journal, year	Chaudhry et al. Survival for waitlisted kidney failure patients receiving transplantation versus remaining on waiting list: systematic review and meta-analysis. BMJ. 2022 (3)
Study type and design	Systematic review and meta-analysis
Sample size (n)	34,467
Main inclusion and exclusion criteria	Chaudhry et al. included all studies comparing mortality between patients with kidney failure deemed suitable for transplant surgery (that is, waitlisted) receiving transplantation versus those remaining on dialysis with minimum one year of follow-up. Chaudhry et al. excluded studies based solely on paediatric populations (age <16 years) or multi-organ transplant recipients, as well as studies with a small cohort size (<30 patients).
Intervention	Renal transplantation
Comparator(s)	Dialysis
Follow-up time	-
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	The main outcome measure was all-cause mortality.
Method of analysis	Meta-analysis was done using the DerSimonian-Laird random effects model, with heterogeneity investigated by subgroup analyses, sensitivity analyses, and meta-regression.
Subgroup analyses	Chaudhry et al. stratified studies by geographical region, donor type and population type.
Other relevant information	None

Table 105: Main characteristics of Sørensen et al. 2016

Trial name: Survival Benefit in Renal Transplantation Despite High Comorbidity	Doi: 10.1097/TP.0000000000001002
Objective	To analyse the chances and survival benefit of transplantation among patients in different age groups and with different degrees of comorbidity score at the time of entering the waiting list

Trial name: Survival Benefit in Renal Transplantation Despite High Comorbidity	Doi: 10.1097/TP.0000000000001002
Publications – title, author, journal, year	Survival Benefit in Renal Transplantation Despite High Comorbidity. Sørensen VR, Heaf J, Wehberg S, Sørensen SS. Transplantation. 2016 Oct;100(10):2160–7
Study type and design	Register study
Sample size (n)	3,174
Main inclusion and exclusion criteria	Not applicable
Intervention	Renal transplantation
Comparator(s)	Dialysis
Follow-up time	The study period was from January 1, 1995, to December 31, 2011
Is the study used in the health economic model?	Yes, in a sensitivity analysis
Primary, secondary and exploratory endpoints	The main outcome measure was all-cause mortality.
Method of analysis	Data was analysed using a multistate model. At any given time after the first waiting list entry, a patient is in one of three main stages: (1) still on the wait list, (2) transplanted with a deceased or a living donor, or (3) dead. A multistate model was used to analyse the chance of having a renal transplantation and the effect of transplantation in different patients groups.
Subgroup analyses	Subgroups according to age and comorbidities
Other relevant information	None

Table 106: Main characteristics of Lee et al. 2005 (56)

Trial name: Characterisation and comparison of health-related quality of life for patients with renal failure	Doi : 10.1185/030079905X65277
Objective	To assess the HRQoL in patients with kidney failure who had received kidney transplants compared to those receiving HD, PD or on waiting list to start dialysis

Trial name: Characterisation and comparison of health-related quality of life for patients with renal failure	Doi : 10.1185/030079905X65277
Publications – title, author, journal, year	Characterisation and comparison of health-related quality of life for patients with renal failure. Lee AJ, Morgan CLI, Conway P, Currie CJ. Current Medical Research and Opinion. 2005 Nov;21(11):1777–83.
Study type and design	The study is a cohort study.
Sample size (n)	416 patients
Main inclusion and exclusion criteria	Patients were identified from the renal unit department database at the University Hospital of Wales.
Intervention	Haemodialysis, peritoneal dialysis and renal transplantation
Comparator(s)	None
Follow-up time	Not applicable
Is the study used in the health economic model?	Yes, for utility values
Primary, secondary and exploratory endpoints	Quality of life (EQ-5D, SF-36, KDQOL)
Method of analysis	Data was analysed using the Wilcoxon Rank test to compare the renal transplant group and the dialysis groups. To compare the EQ-5D index, all treatment groups were age standardised to the transplant group using the direct method.
Subgroup analyses	None
Other relevant information	None

Table 107: Main characteristics of Eriksson et al. 2017 (67)

Trial name: Health-related quality of life across all stages of autosomal dominant polycystic kidney disease	Doi: 10.1186/s12913-017-2513-8
Objective	To assess HRQoL in ADPKD patients across all stages of the disease, from patients with early chronic kidney disease (CKD) to patients with end-stage renal disease
Publications – title, author, journal, year	Health-related quality of life across all stages of autosomal dominant polycystic kidney disease. Daniel Eriksson, Linda Karlsson, Oskar Eklund, Hans Dieperink, Eero Honkanen, Jan Melin, Kristian Selvig and Johan Lundberg6. Nephrol Dial Transplant (2017) 32: 2106–2111
Study type and design	The study was a multi-site cohort study of patients from the Nordic countries involving cross-sectional patient-reported outcomes. .

Trial name: Health-related quality of life across all stages of autosomal dominant polycystic kidney disease	Doi: 10.1186/s12913-017-2513-8
Sample size (n)	EQ-5D-3L responses were available for 124 patients (dialysis 61 and transplant 63).
Main inclusion and exclusion criteria	Patients aged 18 or older who had been managed for AKPKD at the clinic during the past 12 months, had been diagnosed at least 12 months ago, had an eGFR laboratory result available in the past 12 months (not applicable if patient was on dialysis), had not been involved in an investigational clinical trial that resulted in a change in the standard of care received in the past 12 months, if on maintenance dialysis, had initiated dialysis at least 6 months ago and if having a working kidney transplant, had had the date of transplant at least 6 months ago
Intervention	Kidney transplant
Comparator(s)	Dialysis
Follow-up time	Not applicable
Is the study used in the health economic model?	Yes, for utility values in the sensitivity analysis.
Primary, secondary and exploratory endpoints	EQ-5D-3L
Method of analysis	Summary statistics were calculated, including means and SDs for continuous variables and frequency distributions for categorical variables. EQ-5D index scores were estimated using UK, Danish and Swedish value sets.
Subgroup analyses	None
Other relevant information	None

Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

No comparative analysis was conducted in the current application (see rationale in section 7.4). In Table 108, we present baseline characteristics of patients included in Study 14.

Table 108: Baseline characteristics of 17-HMedIdeS-14 (Study 14). Source: Data on file.

		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex	Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age[a]	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median		[redacted]	[redacted]	[redacted]	[redacted]
	Range		[redacted]	[redacted]	[redacted]	[redacted]
Weight[a]	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median		[redacted]	[redacted]	[redacted]	[redacted]
	Range		[redacted]	[redacted]	[redacted]	[redacted]
BMI[a]	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median		[redacted]	[redacted]	[redacted]	[redacted]
	Range		[redacted]	[redacted]	[redacted]	[redacted]
DGF	Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] At the time of enrolment to the feeder study.

DGF=delayed graft function; N=number of patients enrolled; n=number of patients with data; SD=standard deviation.

Comparability of patients across studies

The comparability of patients across the studies was also described in section 7.1. Patients were between 20 and 73 years of age: the mean age of the study population was 60 years for Study 02 and [redacted] years for Study 03, while the mean age of the study population was similar for Study 04 and Study 06 ([redacted] years and [redacted] years, respectively). In the total population from Study 14, the mean age was [redacted]. Study 02 only included one male participant. The other three studies included both men and women. Study 03 included 70% female and 30% male, Study 04 included 46% females and 54% males and Study 06 included 33% females and 67% males. The combined total population from Study 14 included 17 (46%) females and 20 (54%) males. All patients were sensitised, and 41 (89%) patients were highly sensitised (cPRA ≥ 80%), of whom 33 (72%) had a cPRA ≥ 95%.

All phase 2 studies were open-label, uncontrolled studies. Study 02 and Study 03 were with ascending doses, while patients in Study 04 and Study 06 could receive a second dose within 24 hours of the first dose if XM conversion was not achieved. In Study 02, the starting dose of imlifidase was 0.12 mg/kg given by IV infusion over 15 minutes once or twice. The second dose group received one or two doses of 0.25 mg/kg or less. In Study 03 and 06, the starting dose of imlifidase was 0.25 mg/kg given IV over 15 minutes. In Study 03, the dose was given once. Dose escalation was

decided by a data monitoring committee or board in all three studies. Study 04 was a single-dose study in which the starting dose was 0.24 mg/kg given on day 0. Each patient could be given up to two doses of imlifidase, and the second infusion was given within 24 hours of the first infusion. All phase 2 studies except Study 02 had a total follow-up of 180 days (six months). Study 02 had a total follow-up of 64 days.
Please see Appendix C for a more detailed description of the baseline characteristics of patients in the studies.

Comparability of the study populations with Danish patients eligible for treatment

According to two clinical experts, the age of an average sensitised adult kidney transplant patient is 45-50 years. This is similar to the mean age in Study 14, which was 44.5 years. One clinical expert additionally informed that the majority of Danish sensitised patients are women. In Study 03, 70% were female, while 46% and 31% were female in Study 04 and Study 06, respectively. In Study 14, 46% were female. However, we do not expect sex to have an impact on the efficacy of imlifidase. One clinical expert estimated that around 20% of Danish kidney-transplanted patients are overweight (weighing more than 88 kg). In Study 14, which included sensitised or highly sensitised patients, 13% weighed above 88 kg. In the health economic model, the baseline characteristics (age, male-to-female ratio and weight) from Study 14 was applied in the base case, while the average characteristics of the Danish patient population, estimated by the clinical expert, were included in a sensitivity analysis.

Appendix – D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

In Table 109, an overview of all outcomes included in the assessment of the efficacy and safety of imlifidase is presented. In addition, the table includes a description of the validity and clinical relevance of each outcome.

Table 109: Definition, validity and clinical relevance of each outcome included in the assessment of the efficacy and safety of imlifidase

Outcome measure	Definition	Validity	Clinical relevance
DSA elimination and crossmatch conversion	Removal of DSAs and thereby convert a positive CXM test into a negative. Onsite DSAs were measured with solid phase assay systems that were currently in use at the HLA laboratory of each hospital. DSA levels at 2, 6, 24, and 48 h and days 3–7, 14, 21, 28, 64, 90, 120, and 180 post imlifidase infusion were compared with pre-dose levels. Crossmatch tests used locally were flow cytometric crossmatch of T and B cells (fluorescence-activated flow cytometric crossmatch [FACS]) with approximately 250 channel shifts or fewer and CDC crossmatch. Donor and recipient HLA typing was performed using next generation sequencing or polymerase chain reaction sequence-specific methods for HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP antigens.	DSA elimination and crossmatch conversion is a valid outcome in the assessment of imlifidase, as one of the primary treatment goals of imlifidase is elimination of DSA and crossmatch conversion so patients are suitable for kidney transplant. In addition, all four phase two studies included this outcome.	DSA elimination and crossmatch conversion is a clinically relevant outcome measure, as this is the primary treatment goal of imlifidase.
Kidney function	In most studies, kidney function was measured with eGFR calculated with the abbreviated modification of diet in renal disease formula.	We regard kidney function as a valid outcome. The purpose of imlifidase is to make patients eligible for kidney transplant and thus improve kidney function.	Kidney function is a clinically relevant outcome, as the primary aim of a kidney transplant is to ensure patients have a well-functioning kidney.

Outcome measure	Definition	Validity	Clinical relevance
Overall graft survival	Overall graft survival was defined as time from transplantation to graft loss evaluated at 1, 2, 3 and 5 years after first dose of imlifidase. Graft loss was defined as permanent return to dialysis for at least 6 weeks, re-transplantation or transplantectomy. If dialysis was used to define graft loss, the date of graft loss was the first day of the last ongoing dialysis period reported.	We regard overall graft survival as a valid outcome, as this is a way to measure if patients treated with imlifidase receive successful kidney transplants.	Overall graft survival is a clinically relevant outcome, as the primary aim of a kidney transplant is to ensure patients have a well-functioning kidney.
Overall patient survival	Overall patient survival is defined as time from transplantation to death for any cause evaluated at 1, 2, 3 and 5 years. The outcome was analysed the same way as the primary endpoint (graft survival). The following events were censored: withdrawal from the study, evaluation time point (the yearly evaluations), and end of study.	We regard survival as a valid outcome, as this was requested by the DMC.	Patient survival is a clinically relevant outcome to understand the safety of imlifidase followed by kidney transplant.
Quality of life	QoL was measured with the specific kidney disease-related Kidney Disease Quality of Life-Short Form (KDQOL-SF version 1.3). KDQOL-SF includes: the effects of the disease on activities of daily living, work status and social interaction, the effects of the disease on physical and mental health, and one overall health rating item (46). The questionnaire was answered at all visits (1, 2, 3 and 5 years).	The validity of KDQOL-SF was assessed by Manju et al. 2020 (121).	QoL is a critical outcome due to the high disease and treatment burden in patients with CKD.

Results per study

Efficacy results from Study 02, 03, 04, 06 and 14 are presented in Table 110.

Table 110: Efficacy results of imlifidase (data on file)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Results used in the health economic analysis
Outcome		**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Elimination of DSA and crossmatch conversion	Pre-dose	[redacted]	[redacted]	-	-	-	-	-	-	Median DSA levels with 25% and 75% quartiles	No
	Post-dose (24 hours)	[redacted]	[redacted]								
	Post-dose (180 days)	[redacted]	[redacted]								
Kidney function	Pre-dose	[redacted]	[redacted]	-	-	-	-	-	-	Assessed by eGFR, mL/min/1.73m^2. Mean	No

			Estimated absolute difference in effect		Estimated relative difference in effect		Description of methods used for estimation	Results used in the health economic analysis
	Day 7	[redacted]	[redacted]	-			differences are presented as the difference from the pre-dose kidney function.	
	Day 21	[redacted]	[redacted]	-				
	Day 90	[redacted]	[redacted]	-				
	Day 180	[redacted]	[redacted]	-				
	1-year post-dose	[redacted]	[redacted]	-				
	2 years post-dose	[redacted]	[redacted]	-				
	3 years post dosing	[redacted]	[redacted]	-				
Graft survival	0 - 6 months	[redacted]	[redacted]	-	-	-	Death censored graft survival by time period. The	Yes

			Estimated absolute difference in effect		Estimated relative difference in effect			Description of methods used for estimation	Results used in the health economic analysis
	6 months - 1 year	[redacted]						estimates at each time point are for patients who have not experienced graft failure or have died.	
	1 – 2 years	[redacted]						Graft survival is assumed at earlier time points if 'Yes' at a later time point. Due to timing of entry into the studies, not all patients have reached later time points. Upper limit of confidence interval was calculated by dividing 3 with n (3/n), as suggested by the Cochrane handbook (version 5.1.0 (45)). Confidence interval was calculated with Clopper-Pearson's exact method.	
	2 – 3 years	[redacted]							
	3 – 5 years	[redacted]							
Overall survival	0 - 6 months	[redacted]	[redacted]		-	-	-	The estimates at each time point are for patients who have not experienced graft failure or have died.	Yes
	6 months - 1 year	[redacted]							

			Estimated absolute difference in effect		Estimated relative difference in effect				Description of methods used for estimation	Results used in the health economic analysis
	1 – 2 years	[redacted]							Survival is assumed at earlier time points if 'Yes' at a later time point. Because of timing of entry into the studies, not all patients have reached the later time points. Upper limit of confidence interval was calculated by dividing 3 with n (3/n), as suggested by the Cochrane handbook (version 5.1.0 (45)). Confidence interval was calculated with Clopper-Pearson's exact method.	
	2 – 3 years	[redacted]								
	3 – 5 years	[redacted]								
QoL, burden of kidney disease	1 year	[redacted]	-	-	-	-	-	-	KDQOL-SF version 1.3. The estimates are mean (SD).	No
	2 year	[redacted]								
	3 year	[redacted]								
	5 years	[redacted]								
	1 year	[redacted]	-	-	-	-	-	-		

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Results used in the health economic analysis
QoL, symptoms/problems	2 year	[redacted]	[redacted]								
	3 year	[redacted]	[redacted]								
	5 years	[redacted]	[redacted]								
QoL, effect of kidney disease	1 year	[redacted]	[redacted]	-	-	-	-	-	-		
	2 year	[redacted]	[redacted]								
	3 year	[redacted]	[redacted]								
	5 years	[redacted]	[redacted]								
QoL	1 year	[redacted]	[redacted]	-	-	-	-	-	-		
	2 year	[redacted]	[redacted]								
	3 year	[redacted]	[redacted]								
	5 years	[redacted]	[redacted]								

Appendix – E Safety data for intervention and comparator(s)

Safety data for imlifidase from Study 02, Study 03, Study 04 and Study 06 is presented in Table 111 to Table 114.

Table 111: Safety data for Study 02 (NCT02224820)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Active/Chronic AMR	Imlifidase	1	0 (not applicable)	-	-	-	-	-	-	*Confidence intervals were calculated by dividing 3/n, as suggested by the Cochrane handbook (version 5.1.0 (45)). **Confidence intervals were calculated with Clopper-Pearson's exact method.
Subclinical AMR	Imlifidase	1	0 (not applicable)	-	-	-	-	-	-	
Hyperacute rejection	Imlifidase	1	0 (not applicable)	-	-	-	-	-	-	

Table 112: Safety data from Study 03 (NCT02475551)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	

Active/Chronic AMR	Imlifidase	10	3 (30%) 95% CI: 1.6%, 58.4%	-	-	-	-	-	-	*Confidence intervals were calculated by dividing 3/n, as suggested by the Cochrane handbook (version 5.1.0 (45)). **Confidence intervals were calculated with Clopper-Pearson's exact method.
Subclinical AMR	Imlifidase	10	0 (0%) 95% CI: 0.0%, 30.0%*	-	-	-	-	-	-	
Hyperacute rejection	Imlifidase	10	0 (0%) 95% CI: 0.0%, 30.0%*	-	-	-	-	-	-	

Table 113: Safety data for Study 04 (NCT02426684)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	
Active/Chronic AMR	Imlifidase	17	2 (12%) 95% CI: 1.5%, 36.4%**	-	-	-	-	-	-	*Confidence intervals were calculated by dividing 3/n, as suggested by the Cochrane handbook (version 5.1.0 (45)). **Confidence intervals were calculated with Clopper-Pearson's exact method.
Subclinical AMR	Imlifidase	17	1 (6%) 95% CI: 0.1%, 28.7%**	-	-	-	-	-	-	
Hyperacute rejection	Imlifidase	17	1 (6%) 95% CI: 0.1%, 28.7%**	-	-	-	-	-	-	

Table 114: Safety data for Study 06 (NCT02790437)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value	
Active/Chronic AMR	Imlifidase	18	6 (33%) 95% CI: 11.6%, 55.1%	-	-	-	-	-	-	*Confidence intervals were calculated by dividing 3/n, as suggested by the Cochrane handbook (version 5.1.0 (45)). **Confidence intervals were calculated with Clopper-Pearson's exact method.
Subclinical AMR	Imlifidase	18	2 (11%) 95% CI: 1.4%, 34.7%**	-	-	-	-	-	-	
Hyperacute rejection	Imlifidase	18	0 (0%) 95% CI: 0.0%, 16.7%*	-	-	-	-	-	-	

Appendix – F Comparative analysis of efficacy and safety

No comparative analyses were presented in the current application. See rationale in section 7.4.

Appendix – G Extrapolation

Data for graft survival and survival with a functioning graft were obtained from the imlifidase studies 02, 03, 04, 06 and 14 (see section 7.1). Extrapolation of graft survival and survival with a functioning graft were generated from the time-to-event datasets. The graft survival and survival with a functioning graft were generated by fitting parametric models to the Kaplan-Meier curves from the imlifidase trials.

Dialysis survival was extrapolated using the relative risk of death for patients in dialysis compared to the general population in Italy.

Parametric survival models

The following parametric models were fitted to the "graft survival" and "survival with a functioning graft" datasets:

- Exponential
- Generalised gamma
- Gompertz
- Log-logistic
- Log-normal
- Weibull

To determine the parametric models to be used for extrapolation of survival estimates for the standard parametric models, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were considered, as well as the sum of squares (SS). A summary of the AIC and BIC statistics for each parametric model is presented in Table 115.

Table 115: summary of the AIC and BIC and SS statistics for each parametric model

Model	Graft survival					Survival with a functioning graft			
	iBox	Full imlifidase population		Unlikely to be transplanted		Full imlifidase population		Unlikely to be transplanted	
	SS	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]								
Weibull	[redacted]								
Log-normal	[redacted]								
Log-logistic	[redacted]								
Gompertz	[redacted]								
Generalised Gamma	[redacted]								

Graft survival

Three approaches to estimate graft survival over the lifetime of the cost-effectiveness model were considered:

- full imlifidase dataset using data from all 46 patients studied within the imlifidase clinical trials;
- unlikely to be transplanted dataset using data from the subset of highly sensitised patients treated with imlifidase (25 patients); and
- iBox, which is a validated graft prediction model.

Each approach is described in detail below.

Full imlifidase population

The patients in this group were enrolled in the imlifidase studies 02, 03, 04, 06 and 14 (see section (see section 7.1). Death-censored graft survival using data from all 46 patients who underwent a kidney transplant studied within the imlifidase clinical trials showed that 93% of the patients had a functioning graft at six months. This rate remained at [redacted] by the end of the first and second years and decreased to [redacted] by the end of the third year (55). These observed graft survival results were fitted with parametric functions (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma). Figure 23 shows the parametric models and Figure 24 present the hazard functions. Table 116 shows the parameters and goodness-of-fit criteria (as determined by AIC and BIC) for each of the models.

[redacted]

Table 116: Parameters and goodness-of-fit criteria for graft survival, full imlifidase population

Model	AIC	BIC	Parameter	Parameter value
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]

Cholesky decompositions were generated for each of the parametric models. The Cholesky decompositions describe the covariance between model parameters and allow probabilistic modelling of survival curves. The Cholesky decompositions are shown in Table 117.

Table 117: Cholesky decompositions for graft survival, full imlifidase population

Model*	Parameter	Cholesky decompositions	
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

*Variance-covariance for the generalised gamma did not converge and thus could not be included in the PSA.

All functions appear plausible at visual inspection, except for the Gompertz function, which seems to stagnate after approximately 10 years. Visual inspection suggests that the results produced by the generalised gamma and the exponential are the most conservative. The exponential function had the smallest sum in AIC-BIC and was therefore selected as the most plausible curve to represent graft survival in the in the full imlifidase dataset. Moreover, the exponential function was the most conservative function with a converged variance-covariance.

The full imlifidase dataset represents the largest pool of patients treated and is based on observed values. Thus, the full imlifidase dataset was considered to provide the most robust prediction of long-term graft survival and was used as the base case in the CUA model.

Unlikely to be transplanted population

Death-censored graft survival estimates were also produced for the subset of highly sensitised patients treated with imlifidase who were considered "unlikely to be transplanted". In the analysis, this was defined as patients with cPRA ≥95% and positive crossmatch against a deceased donor organ. These data offer the closest match to the patients suitable for imlifidase under its licensed indication. In the observed data from patients who were "unlikely to be transplanted" and who received a transplant with imlifidase, the graft survival at six months was [redacted], and it decreased over time to [redacted] at the end of three years. These observed graft survival results were fitted with parametric functions (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma). Figure 25 shows the parametric models and Figure 26 presents the hazard functions. Figure 25 [redacted]

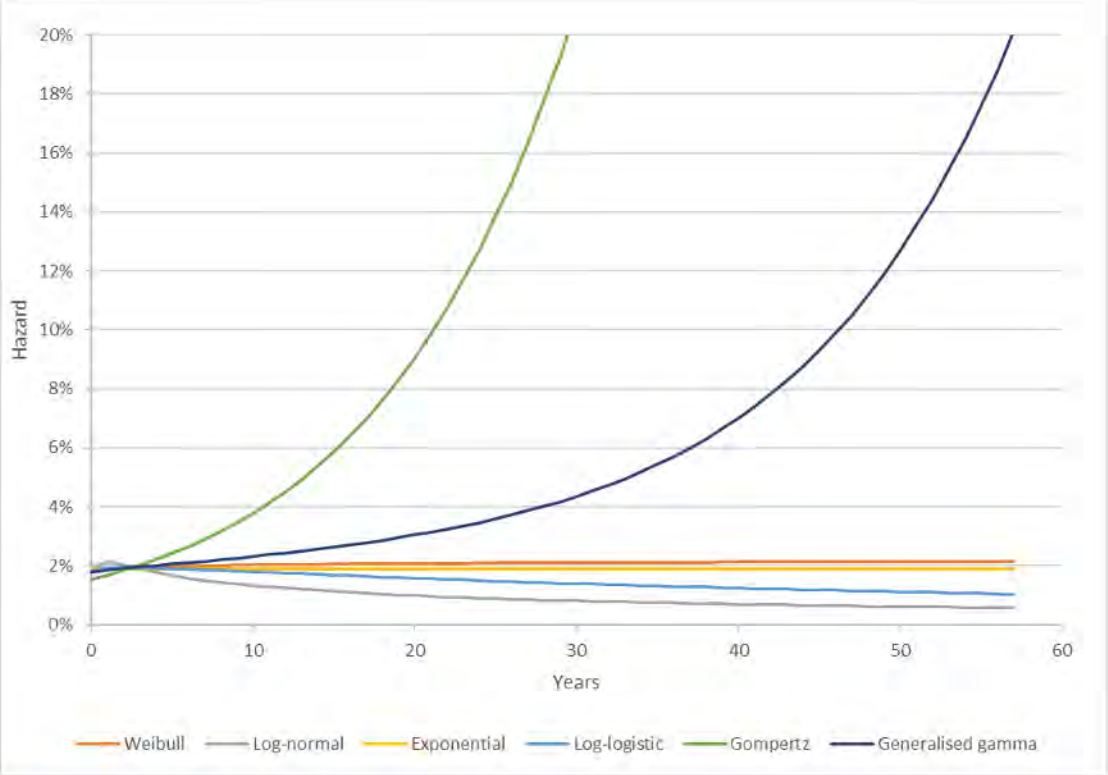


Figure 26: Hazard functions for graft survival predictions and extrapolation, unlikely to be transplanted (data on file)

Table 118 shows the parameters and goodness-of-fit criteria (as determined by AIC and BIC) for each of the models.

[redacted]

Table 118: Parameters and goodness-of-fit criteria for graft survival, unlikely to be transplanted

Model	AIC	BIC	Parameter	Parameter value
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]

Cholesky decompositions were generated for each of the parametric models. The Cholesky decompositions describe the covariance between model parameters and allow probabilistic modelling of survival curves. The Cholesky decompositions are shown in Table 119.

Table 119: Cholesky decompositions for graft survival, unlikely to be transplanted

Model*	Parameter	Cholesky decompositions	
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

*Variance-covariance for the generalised gamma did not converge and thus could not be included in the PSA.

All functions appear plausible at visual inspection, except for the Gompertz function, which reaches 0% graft survival after 20 years. Visual inspection suggests that the results produced by the generalised gamma and Weibull are the most conservative apart from the Gompertz function. The exponential function was placed in the middle in terms of conservativeness and provided the smallest sum in AIC-BIC. As such, the exponential function was selected as the most plausible curve to represent graft survival in the "unlikely to be transplanted" dataset.

The "unlikely to be transplanted" population is the least robust of the populations, as it includes the smallest number of patients. As such, it was not selected for the base case in the CUA model. Nevertheless, this population is the one that most closely matches the target population for this submission, so this was explored as a scenario analysis and included as an option in the model.

iBox

The iBox is an algorithm developed by Professor Alexandre Loupy and team in collaboration with international kidney transplant centres to address the need to predict long-term kidney allograft survival. Currently, kidney allograft survival for all kidney transplant recipients is 90%–95% at one year post-transplant (122); however, graft survival is less predictable beyond the first year due to variability in transplant practice and allograft quality (123,124).

The iBox risk prediction tool was developed and validated in three steps. The first step of development was the creation and internal validation of the algorithm in the derivation cohort. The derivation cohort included 4,000 kidney transplant recipients from four French transplant centres who underwent a kidney transplant between 2005 and 2014 (124). Thirty-two prognostic factors, including donor and recipient parameters as well as parameters collected at the time of evaluation included in the standard of care terms of follow-up (creatinine, proteinuria, DSA and estimated glomerular filtration rate [eGFR] measurement, and biopsy results) (124).

All 32 parameters were evaluated as determinants in a univariate Cox analysis and multivariate Cox model in which eight parameters were identified as independently associated with allograft loss: post-transplant evaluation date, creatinine, proteinuria, DSA, histological parameters (including glomerulitis and peritubular capillaritis; interstitial inflammation and tubulitis; interstitial fibrosis and tubular atrophy; and transplant glomerulopathy (124). The internal

validity of the final model was confirmed by using a bootstrap procedure, which involved generating 1,000 datasets derived from resampling the original dataset (more details in the publication). The accuracy of the prediction model was assessed based on its discrimination ability and calibration performance. The iBox system showed accuracy when assessed at different times of evaluation post-transplant, was validated in different clinical scenarios, including type of immunosuppressive regimen used and response to rejection therapy, and outperformed previous risk-prediction scores as well as a risk score based solely on functional parameters, including eGFR and proteinuria (124). Finally, the accuracy of the iBox risk score in predicting long-term allograft loss was further validated in three randomised controlled trials (124).

Imlifidase dataset

[redacted]

Imlifidase graft survival estimates from iBox

Table 120 summarises the iBox graft survival prediction results from the iBox analysis. The iBox survival predictions were performed on patients with a functioning graft at six months (the evaluation period). At six months, the observed values of the independent predictors of survival were used as inputs to the iBox model.

Table 120: Graft survival post-evaluation, prediction results from iBox

Post-evaluation survival, years	Survival, %
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]

The resulting graft survival estimates from the iBox model are post-evaluation (based on patient characteristics at six months post-transplant). Therefore, the one-year graft post-evaluation survival estimate from the iBox model represents 18 months post-transplant. Subsequently, the two-year graft survival estimate represents 30 months post-transplant, and so on. In the model, the first six-month graft survival estimates are based on the imlifidase observed data from highly sensitised patients who are considered unlikely to be transplanted and who achieved a transplant by receiving imlifidase. Since the iBox graft survival predictions (Table 120) do not consider graft loss that occurs between transplant and six months, they were multiplied by the proportion of patients with a functioning graft at six months (first cycle of the model). [redacted]

of these patients had a functioning graft at six months. Applying the iBox predicted graft survival at one year [redacted] who entered the model will still have a graft at cycle 3 (18 months post-transplant). Table 121 shows the graft survival used in the CUA model derived from the survival at six months in the observed data and the iBox survival predictions at each year.

Table 121: Model graft survival

Model cycle (6 months)	Years post-transplant	Graft survival
0	0	[redacted]
1	0.5	[redacted]
3	1.5	[redacted]
5	2.5	[redacted]
7	3.5	[redacted]
9	4.5	[redacted]
11	5.5	[redacted]
13	6.5	[redacted]
15	7.5	[redacted]
17	8.5	[redacted]
19	9.5	[redacted]
21	10.5	[redacted]

The predicted graft survival from Table 120 was fitted with parametric functions, and the extrapolations from the exponential, Weibull, log-normal, and log-logistic, Gompertz and generalised gamma are shown against the iBox predictions in Figure 27. Table 122 shows the parameters and goodness-of-fit criteria (as determined by SS) for each of the models.

[redacted]

Table 122: Parameters and goodness-of-fit criteria for graft survival, iBox

Model	SS	Parameter	Parameter value
Exponential			
Weibull			
Log-normal			
Log-logistic			
Gompertz			
Generalised Gamma			

All functions appear plausible at visual inspection. It was not possible to generate the AIC and BIC for the iBox, because the data were not extrapolated using individual patient data. They were extrapolated based on the iBox predictions at 10 different time points. In the model, a solver was used for each of the functions to determine the function coefficients and the method of the sum of least square was used to determine which of the functions was the best fit (Table 115). For the

same reason, there are no variance-covariance matrix associated with iBox. The generalised gamma function presented the best fit, as it was associated with the smallest sum of least squares.

As the iBox survival estimates are not based on actual graft survival data, and because there is no variance-covariance matrix associated with iBox, we did not use it as the base case in the CUA model. Instead, it was included as a scenario analysis.

Comparison of the three graft survival scenarios

Figure 29 shows the selected predictions for the three survival scenarios explored above (i.e., "full imlifidase dataset", "unlikely to be transplanted dataset" and "iBox model"). The data show that the three model scenarios give predictions that are quite similar, with the two imlifidase treatment-based predictions based on historical data resulting in almost identical survival estimates and the iBox prediction being the most conservative of the three.

Abbreviations: UT: unlikely to be transplanted.
Note: The full imlifidase extrapolation and "UT" estimates are so close that it is hard to distinguish both lines.

The imlifidase three-year follow-up trial data is robust and relevant. The indication for this application to the DMC is classed as rare; therefore, the trials are consequently small in numbers. Imlifidase was studied in 46 transplanted patients, which is by no means limited for phase 2 development in orphan diseases.

The significant unmet medical need in the licensed indication supported the EMA's decision to grant a conditional marketing authorisation based on this same phase 2 data. Hansa recognises that the evidence will be further strengthened when the phase 3 PAES study is conducted. However, the efficacy and safety of imlifidase were deemed enough to grant conditional marketing approval, and the indicated patients currently have no access to kidney transplantation, and their only prospect is to remain on long-term dialysis, which has a significant negative impact on healthcare cost, mortality and quality of life.

The three-year data published last year are in fact the longest-term clinical trial data in the area of highly sensitised kidney transplantations. This makes the trial data highly relevant and important. The uncertainty is diminished by the fact that the efficacy and safety of imlifidase are consistent; irrespective of the subgroup, imlifidase enables the transplantation.

It is widely accepted that long-term allograft survival is impacted by multiple variables, including (but not limited to) medication non-adherence, donor graft quality, ischemic reperfusion injury, comorbid conditions and the original cause of kidney failure. Therefore, it is difficult to compare the potential outcomes of patients who receive an imlifidase-enabled kidney transplant to any other cohort than the true standard of care, which are patients currently awaiting a compatible organ offer while on dialysis. Therefore, the iBox graft survival extrapolation is a relevant scenario to validate the three-year-follow-up base case against. When comparing the five-year and 10-year survival estimates from the two most recent UK data sources published (NHSBT Annual report data (125) and a paper published last summer by Krishnan et al. 2021 at University Hospital Coventry and Warwickshire (UHCW) hospital on incompatible transplantations (126)) with the iBox projections, five-year and 10-year graft survival rates are all higher than the iBox extrapolations.

Estimates from these studies, together with the iBox prediction and the extrapolation based on the data from the clinical studies, are presented in Table 123.

Table 123: Comparison of long-term graft survival.

Source	Graft survival	
	5 years	10 years
NHSBT 2007-2009, DCD [1]	0.86	0.75
NHSBT 2013-2015, DCD [1]	0.86	-
NHSBT 2007-2009, DBD [1]	0.85	0.74
NHSBT 2013-2015, DBD [1]	0.87	-
Krishnan et al, 2021, HLAi cohort [2]	0.85	0.70
[redacted]	[redacted]	[redacted]
All imlifidase extrapolations – 3-year follow-up data	0.82	0.68
UTT imlifidase extrapolations – 3-year follow-up data	0.83	0.68

Patient survival with a functioning graft

Two approaches to estimate survival with a functioning graft were considered:

- full imlifidase dataset using data from all 46 patients studied within the imlifidase clinical trials; and
- unlikely to be transplanted dataset using data from the subset of highly sensitised patients treated with imlifidase (25 patients).

Each approach is described in detail below.

Full imlifidase population

Patients in the full imlifidase population were all alive six months after transplant. At the end of the first year, 92% of patients were alive, and this [redacted] These patient survival results were fitted with parametric functions (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma). Figure 30 shows the parametric models and Figure 31 presents the hazard functions. Table 124 shows the parameters and goodness-of-fit criteria (as determined by AIC and BIC) for each of the models.

[redacted]

Table 124: Parameters and goodness-of-fit criteria for patient survival with a functioning graft, full imlifidase population

Model	AIC	BIC	Parameter	Parameter value
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]

Cholesky decompositions were generated for each of the parametric models. The Cholesky decompositions describe the covariance between model parameters and allow probabilistic modelling of survival curves. The Cholesky decompositions are shown in Table 125.

Table 125: Cholesky decompositions for survival with a functioning graft, full imlifidase population

Model*	Parameter	Cholesky decompositions	
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

* Variance-covariance for the generalised gamma did not converge and thus could not be included in the PSA.

All functions appear plausible at visual inspection, except for the Gompertz function, which seems to stagnate after approximately three years. Visual inspection suggests that the results produced by the exponential function were the most conservative. The exponential distribution was also considered the best fit based on the AIC and BIC criteria, as shown in Table 124. Thus, the exponential function was selected as the most plausible curve to represent survival with a functioning graft in the full imlifidase dataset.

The full imlifidase dataset represents the largest pool of patients treated and is based on observed values. Thus, the full imlifidase dataset was considered to provide the most robust prediction of long-term survival with a functioning graft and was used as the base case in the CUA model.

Unlikely to be transplanted population

In the analysis, "unlikely to be transplanted" was defined as patients with cPRA ≥95% and positive crossmatch against a deceased donor organ. All patients with a functioning graft from the "unlikely to be transplanted" population were alive at six months after transplant, and 84% remained alive at the end of the third year. The observed patient survival results were fitted with parametric functions (exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma). Figure 32 shows the parametric models and Figure 33 presents the hazard functions. Table 126 shows the parameters and goodness-of-fit criteria (as determined by AIC and BIC) for each of the models.

Table 126: Parameters and goodness-of-fit criteria for patient survival with a functioning graft, unlikely to be transplanted

Model	AIC	BIC	Parameter	Parameter value
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]

Cholesky decompositions were generated for each of the parametric models. The Cholesky decompositions describe the covariance between model parameters and allow probabilistic modelling of survival curves. The Cholesky decompositions are shown in Table 127.

Table 127: Cholesky decompositions for survival with a functioning graft, unlikely to be transplanted

Model*	Parameter	Cholesky decompositions	
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

*Variance-covariance for the generalised gamma did not converge and thus could not be included in the PSA.

At visual inspection, the exponential, Weibull, log-normal and log-logistic function all seem plausible, while the Gompertz and generalised gamma functions seem to stagnate after approximately four and 20 years, respectively. Visual inspection suggests that the results produced by the exponential function is the most conservative. The exponential distribution was also considered the best fit based on the AIC and BIC criteria, as shown in Table 126. Thus, the exponential function was selected as the most plausible curve to represent survival with a functioning graft in the "unlikely to be transplanted" dataset.

The "unlikely to be transplanted" population is the least robust of the populations considered because it includes the smallest number of patients. As such, it was not selected for the base case in the CUA model. Nevertheless, this population is the one that most closely matches the target population for this submission, so this was explored as a scenario analysis and included as an option in the model.

[redacted]**Compares the scenarios in the model for patient survival with a functioning graft (based on extrapolations from the full imlifidase population and "unlikely to be transplanted" population with the overall patient survival of HLA-incompatible live donor and DD transplant from Pankhurst et al. 2017 (127).**

There is an important difference between the data used in the model and the sources considered here: in the imlifidase populations, patients are censored when they lose their graft, and only survival with a functioning graft is considered in the predicted survival. However, the data from Pankhurst et al. 2017 considered overall survival; patients were followed whether they lose their graft or not. As a result, the curve based on Pankhurst et al. 2017 data shows survival rates that are lower than what they would be if only the survival with a functioning graft was shown. We can see from the graph that the full imlifidase population curve over three years is close to Pankhurst et al. 2017 data curves and aligns well with the latter results by year 5, while the extrapolation using the "unlikely to be transplanted" population shows lower patient survival estimates over the five years.

Dialysis survival

Despite an abundance of literature related to dialysis, only one study was included based on the SLR in relation to dialysis survival (see section 6). This study was Chaudry et al. 2022 (3) investigated the survival benefit of transplantation versus dialysis in 34,467 patients from multiple countries in Europe who have undergone renal transplantation or who are on dialysis and are on waiting list for a transplant. The meta-analysis provides a pooled HR for long-term, all-cause mortality at 0.49 for the transplantation group, compared with the dialysis group in the European study population. This study was used to inform dialysis survival in the model.

From Chaudhry et al. 2022 (3), we identified Sørensen et al. 2016 (41), who merged data from the Danish Nephrology Registry and Scandiatransplant between January 1995 and December 2011 to study the survival gains associated with kidney transplant. Controlling for cohort, age, sex, renal diagnosis and time on dialysis before entering, the study estimates significant reduction in the risk of death for patients receiving kidney transplantation (HR=0.38). We apply this HR to study the impact on survival in the sensitivity analyses. Also, the impact of applying tranplantation mortality rates from the study by Boenink 2020 to model survival with a functioning graft and dialysis was assessed in a scenario analysis.

The HRs from these sources were applied to the OS curve for patients with a functioning graft in order to obtain the OS curve for patients on dialysis treatment.

Figure 11 shows the age-specific survival for kidney-transplanted patients and for patients in dialysis treatment applying the HR published in Chaudhry et al. 2022 and Sørensen et al. 2016.

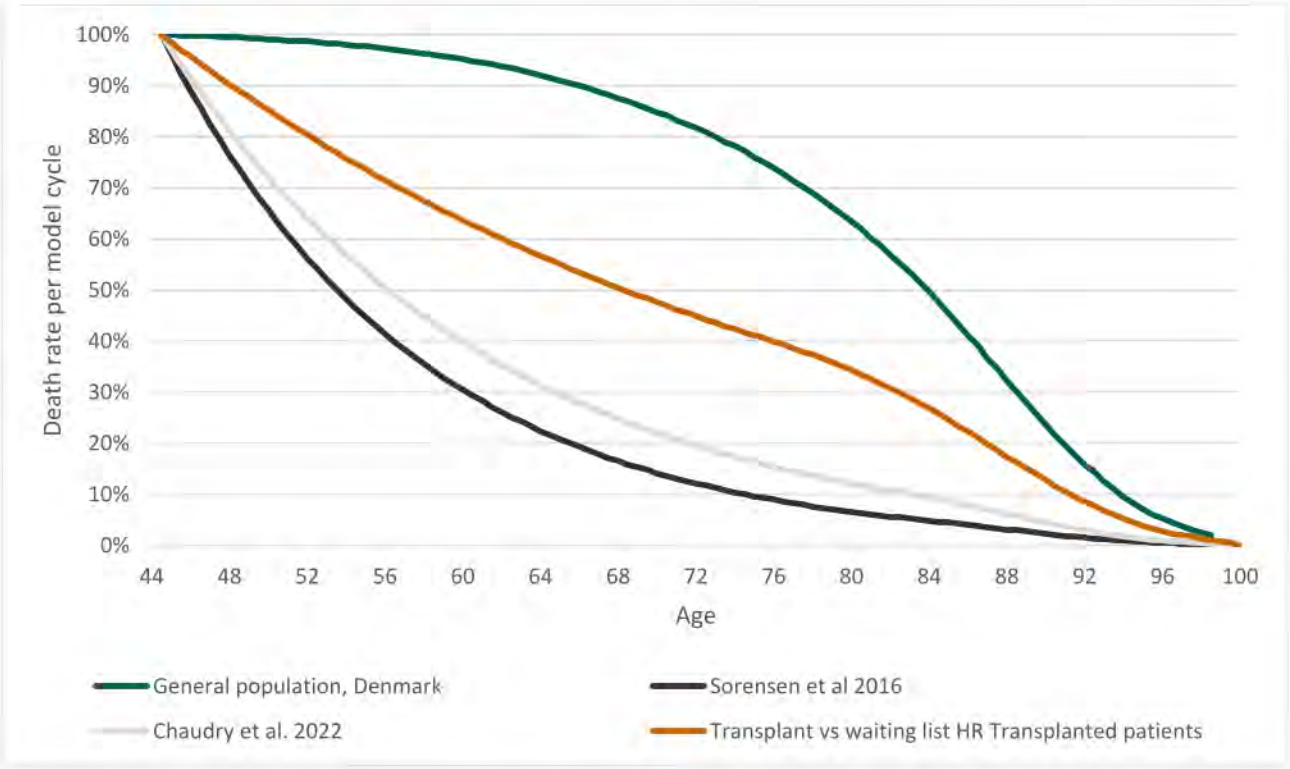


Figure 35: Comparison of survival for dialysis patients with kidney transplanted patients and for the general population and dialysis patients in Denmark

Appendix H – Literature search for HRQoL data

The literature search for HRQoL data is presented in Appendix A.

Appendix I Mapping of HRQoL data

Mapping of HRQoL data was not carried out for this assessment.

Appendix J Probabilistic sensitivity analyses

	Expected value	Standard error	Probability distribution	Parameter distribution	Parameter distribution	Refers to cell (in the Excel model)
Imlifidase treatment						
Proportion of patients requering 1 vial	[redacted]	[redacted]	[redacted]			Costs!P12
Proportion of patients requering 2 vials	[redacted]	[redacted]	[redacted]			Costs!P13
Proportion of patients requering 3 vials	[redacted]	[redacted]	[redacted]			Costs!P14
Proportion requiering a second dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Costs!P18
Patient population						
Initial age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Clinical!P11
Proportion of females	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Clinical!P12
Imlifidase extrapolations						
Imlifidase graft survival	[redacted]	[redacted]	[redacted]			Clinical!K19
Imlifidase patient survival	[redacted]	[redacted]	[redacted]			Clinical!K27
Dialysis						
Proportion of haemodialysis patients	80.4%	8.0%	Beta	α: 20	β: 5	Costs!P54
Death: from dialysis: HR vs transplant, Chaundry 2022	2.04	0.103	Normal			Clinical!N35
Imlifidase-related AEs						
Pneumonia	5.6%	0.6%	Beta	α: 94	β: 1,606	AEs!P11
Sepsis	3.7%	0.4%	Beta	α: 96	β: 2,504	AEs!P12
Abdominal infection	1.9%	0.2%	Beta	α: 98	β: 5,202	AEs!P13

	Expected value	Standard error	Probability distribution	Parameter distribution	Parameter distribution	Refers to cell (in the Excel model)
Catheter site infection	1.9%	0.2%	Beta	α: 98	β: 5,202	AEs!P14
Parvovirus infection	1.9%	0.2%	Beta	α: 98	β: 5,202	AEs!P15
Upper respiratory tract infection	1.9%	0.2%	Beta	α: 98	β: 5,202	AEs!P16
Infusion-related reaction	1.9%	0.2%	Beta	α: 98	β: 5,202	AEs!P17
Myalgia	1.9%	0.2%	Beta	α: 98	β: 5,202	AEs!P18
Transplant AEs						
AMR (Cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AEs!P23
AMR (Cycle 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AEs!P24
Delayed graft function (Cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AEs!P25
Dialysis AEs						
All-cause infections (PD patients)	0.8%	0.1%	Beta	α: 99	β: 12,121	AEs!R31
All-cause infections (HD patients)	1.2%	0.1%	Beta	α: 99	β: 7,967	AEs!R32
Cardiovascular events (PD patients)	1.3%	0.1%	Beta	α: 99	β: 7,750	AEs!R33
Cardiovascular events (HD patients)	1.2%	0.1%	Beta	α: 99	β: 7,964	AEs!R34
HSUV – Utilities						
Functioning graft	0.710	0.019	Gamma	α: 1,445	β: 0.000	Utilities!P26
Dialysis – HD	0.440	0.032	Gamma	α: 187	β: 0.002	Utilities!P28
Dialysis – PD	0.530	0.043	Gamma	α: 156	β: 0.003	Utilities!P29
Imlifidase costs						
Cost of imlifidase-specific comedication	DKK 28	DKK 3	Gamma	α: 100	β: 0.27608	Costs!P21
Dialysis costs						

	Expected value	Standard error	Probability distribution	Parameter distribution	Parameter distribution	Refers to cell (in the Excel model)
Dialysis weighted average cost per cycle	DKK 198,042	DKK 19,804	Gamma	α: 100	β: 1,980	Costs!P55
Cost of transportation	DKK 8,214	DKK 821	Gamma	α: 100	β: 82	Costs!P56
Cost of patient time	DKK 64,092	DKK 6,409	Gamma	α: 100	β: 641	Costs!P57
Cost of home dialysis training	DKK 4,823	DKK 482	Gamma	α: 100	β: 48	Costs!P58
Cost of patient time related to training	DKK 2,161	DKK 216	Gamma	α: 100	β: 22	Costs!P59
Cost of transportation related to training	DKK 257	DKK 26	Gamma	α: 100	β: 3	Costs!P60
Cost of a kidney transplant						
Transplant procedure cost	DKK 302,156	DKK 30,216	Gamma	α: 100	β: 3,022	Costs!P62
Transplant immunosuppressant costs (0-6 months)	DKK 44,168	DKK 4,417	Gamma	α: 100	β: 442	Costs!P63
Transplant immunosuppressant costs (7-12 months)	DKK 26,451	DKK 2,645	Gamma	α: 100	β: 265	Costs!P64
Transplant immunosuppressant costs (Sub years)	DKK 26,524	DKK 2.652	Gamma	α: 100	β: 265	Costs!P65
Transplant maintenance cost (0-6 months)	DKK 27,270	DKK 2.727	Gamma	α: 100	β: 273	Costs!P66
Transplant maintenance cost (7-12 months)	DKK 9,090	DKK 909	Gamma	α: 100	β: 91	Costs!P67
Transplant maintenance cost per cycle (Sub years)	DKK 4,469	DKK 447	Gamma	α: 100	β: 45	Costs!P68
Cost of transportation (0-6 months)	DKK 2,660	DKK 266	Gamma	α: 100	β: 27	Costs!P69

	Expected value	Standard error	Probability distribution	Parameter distribution	Parameter distribution	Refers to cell (in the Excel model)
Cost of transportation (7-12 months)	DKK 840	DKK 84	Gamma	α: 100	β: 8	Costs!P70
Cost of transportation per cycle (Sub years)	DKK 280	DKK 28	Gamma	α: 100	β: 3	Costs!P71
Cost of patient time (0-6 months)	DKK 87,604	DKK 8,760	Gamma	α: 100	β: 876	Costs!P72
Cost of patient time (7-12 months)	DKK 1,629	DKK 163	Gamma	α: 100	β: 16	Costs!P73
Cost of patient time per cycle (Sub years)	DKK 543	DKK 54	Gamma	α: 100	β: 5	Costs!P74
End-of-life cost						
End-of-life cost	DKK 74,804	DKK 7,480	Gamma	α: 100	β: 748	Costs!P75
Imlifidase adverse event costs						
Pneumonia	DKK 35,491	DKK 3,549	Gamma	α: 100	β: 355	Costs!P124
Sepsis	DKK 45,361	DKK 4,536	Gamma	α: 100	β: 454	Costs!P125
Abdominal infection	DKK 35,699	DKK 3,570	Gamma	α: 100	β: 357	Costs!P126
Catheter site infection	DKK 31,420	DKK 3,142	Gamma	α: 100	β: 314	Costs!P127
Parvovirus infection	DKK 40,002.	DKK 4,000	Gamma	α: 100	β: 400	Costs!P128
Upper respiratory tract infection	DKK 52,911.	DKK 5,291.	Gamma	α: 100	β: 529	Costs!P129
Infusion-related reaction	DKK 0	DKK 0	Gamma	-	-	Costs!P130
Myalgia	DKK 0	DKK 0	Gamma	-	-	Costs!P131
Transplant AEs costs						
AMR	DKK 339,084	DKK 33,908	Gamma	α: 100	β: 671	Costs!P134

	Expected value	Standard error	Probability distribution	Parameter distribution	Parameter distribution	Refers to cell (in the Excel model)
Delayed graft function (Cycle 1)	DKK 23,922	DKK 2,392	Gamma	α: 100	β: 239	Costs!P135
Graft Loss (Cycle 1)	DKK 49,020	DKK 4,902	Gamma	α: 100	β: 490	Costs!P136
Graft Loss (Cycle 2)	DKK 32,540	DKK 3,254	Gamma	α: 100	β: 325	Costs!P137
Graft Loss (Cycle 3)	DKK 20,136	DKK 2,014	Gamma	α: 100	β: 201	Costs!P138
Graft Loss (Cycle 4)	DKK 20,136	DKK 2,014	Gamma	α: 100	β: 201	Costs!P139
Graft Loss (Cycle 5+)	DKK 15,706	DKK 1,571	Gamma	α: 100	β: 157	Costs!P140
Dialysis AEs costs						
All-cause infections (PD patients)	DKK 84,139	DKK 8,414	Gamma	α: 100	β: 841	Costs!P143
All-cause infections (HD patients)	DKK 84,139	DKK 8,414	Gamma	α: 100	β: 841	Costs!P144
Cardiovascular events (PD patients)	DKK 31,725	DKK 3,173	Gamma	α: 100	β: 317	Costs!P145
Cardiovascular events (HD patients)	DKK 31,725	DKK 3,173	Gamma	α: 100	β: 317	Costs!P146