NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Hansa Biopharma

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Kidney Research UK
   b. NHS Blood and Transplant,
   c. Renal Association UK

4. **Evidence Review Group report** prepared by Peninsula Technology Assessment Group (PenTAG)

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from Hansa Biopharma

7. **Technical engagement responses and personal perspectives from experts:**
   a. Richard Ayres – patient expert, nominated by Kidney Care UK
   b. Dr Colin Geddes – clinical expert, nominated by nominated by the Renal Association
   c. Dr Sunil Kumar Daga – clinical expert, nominated by British Transplantation Society
   d. Dr Nicholas Torpey – clinical expert, nominated by British Transplantation Society

8. **Technical engagement response from consultees and commentators:**
   a. British Transplantation Society
   b. NHS Blood and Transplant

9. **Evidence Review Group critique of company response to technical engagement** prepared by Peninsula Technology Assessment Group (PenTAG)
   a. ERG report
   b. ERG addendum Revised Section 6 of ERG Report following the

technical engagement response

10. **Letter from NICE to the company requesting additional information**

11. **Company response to NICE request for additional information** from Hansa Biopharma

12. **Company additional information submission** from Hansa Biopharma
    a. Updated company submission
    b. NHSBT Data provide to Hansa
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13. **Clarification questions following first committee meeting and company responses**

14. **Evidence Review Group critique of company response** prepared by PenTAG

15. **Evidence Review Group report – factual accuracy check**

16. **ERG response to NICE request for additional analyses**

17. **Additional submission from Richard Ayres** – patient expert, nominated by Kidney Care UK

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Document B

Company evidence submission

September 2020

File name	Version	Contains confidential information	Date
Imlifidase Document B	1.1	No (redacted)	24 September 2020

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem and the approach taken to it in this submission is summarised in Table 1.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with chronic kidney disease awaiting a kidney transplant from a donor, who are highly sensitised with HLA and have a positive crossmatch with the donor	Adults with chronic kidney disease awaiting a kidney transplant from a deceased donor, who are highly sensitised with HLA, have a positive crossmatch with the donor and are unlikely to be transplanted under the kidney offering scheme	Decision problem is more restricted due to the approved indication for imlifidase
Intervention	Imlifidase	As per the scope	–
Comparator(s)	Established clinical management without imlifidase: • Kidney transplant (may include plasma exchange) • Haemodialysis/haemodiafiltration or peritoneal dialysis	Established clinical management without imlifidase: • Haemodialysis/haemodiafiltration or peritoneal dialysis	Dialysis is the only alternative treatment option available to the population of interest, as they are defined as being unlikely to be transplanted due to their sensitisation and have a positive crossmatch that is a contraindication to transplant
Outcomes	The outcome measures to be considered include: • Efficacy on crossmatch conversion (ability to create a negative crossmatch test in people who exhibit donor specific antibodies) • Mortality • Kidney function (eGFR) • Time to graft failure • Time to rejection; type of rejection; number of rejection episodes • Time to next renal replacement therapy; type of next renal replacement therapy	The outcome measures to be considered include: • Efficacy on crossmatch conversion (ability to create a negative crossmatch test in people who exhibit donor specific antibodies) • Donor specific antibody levels post-transplant/imlifidase treatment • Kidney function • Survival of patients (mortality) • Survival of graft (graft failure) • AMR events	Outcomes presented are those where clinical data are available from clinical trials of imlifidase and prioritised to clearly show the safety and efficacy of imlifidase

	• Time to rebound concentration of donor specific antibodies post-transplant; proportion of patients who require treatment of rebound antibodies post-transplant • Incidence of viral and bacterial infections • Hospitalisation days • Adverse effects of treatment • Health-related quality of life	• Incidence of viral and bacterial infections	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Recipients of kidneys from living donors • Recipients of kidneys from deceased donors • Low risk ('delisted') recipients of donor kidneys, non-delisted recipients of donor kidneys; • Degree of sensitisation in terms of antibody levels (e.g. positive microbead test, flow cytometry crossmatch, positive CDC crossmatch)	No specific subgroups will be considered in this submission	Given the indication, deceased donors are the main population of interest. The other listed subgroups fall outside the indication for imlifidase (living donor transplants, need for a positive crossmatch precludes 'delisted' recipients). The degree of sensitisation is not considered appropriate to subdivide beyond 'highly sensitised' (which form the main population for this appraisal) as the judgement of sensitisation is a complex area that requires clinical judgement around the patient-specific immunological profile. In addition, the SmPC for imlifidase cautions against use in patients with a T-cell CDC crossmatch positive. The company would not like to, with current evidence, recommend this population for imlifidase-enabled kidney transplantation. Therefore, further subgroups based on degree of sensitisation were not considered

			appropriate.
Special considerations including issues related to equity or equality	The equality impact assessment scoping identified the following issues, according to the principles of the NICE equality scheme: • People who are highly sensitised (that is, people on the waiting list for organ transplantation carrying antibodies to HLA) may not be provided with the same access to transplantation and standard of care as non-sensitised people. Imlifidase may help to ensure that this gap can be narrowed further in the future. • Imlifidase may also offer highly sensitised patients in minority ethnic groups, who already have difficulty accessing a matched donor kidney. These people with protected characteristics could gain access to a donor kidney sooner and, thus, are likely to have better outcomes once transplanted. • Clinical experts at the scoping workshop indicated that one of the most common causes for a patient to be 'highly sensitised' is previous pregnancy.	As per NICE documents	The evidence around equality issues and groups that may be impacted by the availability of imlifidase will be presented

AMR: antibody-mediated rejection; CDC: complement dependent cytotoxicity; eGFR: estimated glomerular filtration rate; HLA: human leucocyte antigen

B.1.2 Description of the technology being appraised

Imlifidase is a selective immunoglobulin G (IgG) endopeptidase that rapidly and specifically cleaves and inactivates IgG. Imlifidase is indicated for the desensitisation of people with chronic kidney disease (CKD) whom are highly sensitised with antibodies to human leucocyte antigens (HLA) and who have a positive crossmatch against an available deceased donor kidney. Imlifidase has both EU Orphan Drug Designation for the prevention of graft rejection following solid organ transplant,[1] and PRIority MEdicine (PRIME) designation,[2] an EMA programme to enhance support for the development of medicines that target an unmet medical need (in this case, the unmet medical need in highly sensitised patients who cannot receive a kidney transplant since there is no efficient authorised treatment for the cleavage of IgG, which was combined with the available Phase II results showing imlifidase achieved an efficient and rapid cleavage of IgG).

Table 2 Technology being appraised[3]

UK approved name and brand name	Idefirix™ (imlifidase)
Mechanism of action	Imlifidase is an IgG endopeptidase derived from *Streptococcus pyogenes* that cleaves IgG molecules at the lower hinge region to create F(ab)'2 and Fc fragments. Intact human IgG, regardless of isotype, is cleaved by imlifidase in two steps:[4,5] 1. Single cleavage of the IgG molecule leaving one heavy chain intact 2. Generates a fully cleaved molecule that cannot mediate CDC or antibody-dependent cell-mediated cytotoxicity by means of Fc gamma receptors Imlifidase can cleave soluble IgG as free protein or bound to a specific antigen. It can also cleave cell-associated IgG that is bound through the Fc gamma receptor or as part of the B-cell receptor complex.[4] Therefore, imlifidase is able to cleave IgG in both intravascular and extravascular spaces.
Marketing authorisation/ CE mark status	Imlifidase currently has marketing authorisation in the UK. A positive Committee for Human Medicinal Products was received on 25 June 2020, with conditional marketing authorisation approval received on 25 August 2020.
Indications and any restriction(s) as described in the summary of	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.

product characteristics (SmPC)	Imlifidase is contraindicated in patients with: • Hypersensitivity to the active substance or to any of the excipients • Ongoing serious infection • Thrombotic thrombocytopenic purpura (patients with this blood disorder may be at risk of developing serum sickness) Infusion-related reactions have been reported with imlifidase. If any serious allergic or anaphylactic reaction occurs, imlifidase therapy should be discontinued immediately and appropriate therapy initiated. Mild or moderate infusion-related reactions can be managed by temporarily interrupting the infusion, and/or by administration of medicinal products, such as antihistamines, antipyretics and corticosteroids. An interrupted infusion can be restarted when the symptoms have abated. Imlifidase is a cysteine protease that specifically cleaves IgG. As a consequence, IgG-based medicinal products may be inactivated if given in connection with imlifidase. Antibody-based medicinal products cleaved by imlifidase include, but are not limited to, basiliximab, rituximab, alemtuzumab, adalimumab, denosumab, belatacept, etanercept, rabbit anti-thymocyte globulin and IVIg. IVIg may contain neutralising antibodies against imlifidase, which may inactivate imlifidase if IVIg is given before imlifidase. The SmPC includes recommended time intervals between imlifidase and other antibody-based therapies.
Method of administration and dosage	Imlifidase is provided as freeze-dried (lyophilised) powder (11mg per vial) which is reconstituted in 1.2mL sterile water to form a 10mg/mL concentrate (1.1mL of useable volume). It is recommended that the reconstituted solution is transferred immediately to the infusion bag. The calculated volume of reconstituted concentrate is added to an infusion bag containing 50mL of 0.9% sodium chloride infusion solution. The entire, fully diluted infusion should be administered over a period of 15 minutes and must be administered with an infusion set and a sterile, inline, non-pyrogenic, low protein binding filter (pore size of 0.2µm). Following administration it is recommended that the intravenous line is flushed with infusion fluid to ensure administration of the complete dose. Imlifidase should be administrated at a dose of 0.25mg/kg, within 24 hours prior to transplantation. One dose is adequate for crossmatch conversion in the majority of patients but if needed a second dose can be administered within 24 hours after the first dose.
Additional tests or investigations	Imlifidase will require the use of crossmatch tests to confirm crossmatch conversion before transplant. These tests form part of the current standard of care for transplant and so do not represent additional tests.
List price and average cost of a course of treatment	The proposed list price for imlifidase is £135,000 per vial. Using an estimate based on clinical trial data that [redacted]% require 1 vial, [redacted]% require 2 vials and [redacted]% require 3 vials; in addition [redacted]% of trial patients required a second dose to achieve sufficient elimination of DSA. Considering all these factors, an average

	course of treatment is expected to cost £300,490.
Patient access scheme (if applicable)	A simple patient access scheme has been submitted to PASLU that would apply to imlifidase. This PAS makes imlifidase available with a discount of [redacted]% on list price (equivalent to a cost of £[redacted] per vial. Using the same assumptions as above, this would lead to an average course of treatment costing £[redacted].

DSA: donor specific antibodies; IgG: immunoglobulin G; IVIg: intravenous immunoglobulin

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 End stage kidney disease and renal transplant

CKD is a common condition that affects around 1 in 1000 of the population.[6] The Kidney Disease Improving Global Outcomes (KDIGO) classifies stages of CKD based on cause, glomerular filtration rate (GFR) category, and albuminuria (based on albumin-to-creatinine ratio [ACR]) category; [7] and this classification is replicated within NICE clinical guidelines for CKD.[8] End stage renal disease (ESRD) occurs when CKD has progressed to a level where kidney function is less than 10% of capacity and is associated with Stage 4 (15–29ml/min/1.73m^2) or Stage 5 (<15ml/min/1.73m^2) GFR categories.[7,8] In ESRD patients, the kidneys are unable to carry out required daily functions and renal replacement therapy (RRT) will be considered for these patients.

When estimating the prevalence and incidence of ESRD, focusing on patients undergoing RRT (including both dialysis and kidney transplant) is a useful proxy and provides an evaluation of the population undergoing active treatment. Data from the UK Renal Registry (UKRR) can provide prevalence and incidence rates for RRT.[9] Using the most recently published annual report shows that in England in 2017, there were 54,773 patients receiving RRT, which gave a crude prevalence rate of 985 per million population.[9] The prevalent population has been increasing by 3% per year since 2013 (earliest data included within the report).[9] Of these patients, it was reported that 23,646 were receiving dialysis (20,574 haemodialysis and 3072 peritoneal dialysis).[9] It was also reported that RRT was initiated in 6771 patients in 2017, which gave a crude incidence rate of 122 per million population.[9] The incident

population for RRT has consisted of around 6000 to 7000 per year over the five years of data included in the report.[9]

In patients with ESRD, kidney transplant is seen as the preferred treatment option compared to the alternative of dialysis.[10] Without transplantation, there is no way to reverse the damage to the kidney and so dialysis is usually for life in these patients.[11,12] Kidney transplant has been accepted to increase patient survival and quality of life (as described within the NICE pathway for CKD).[13] The NICE pathway for CKD also notes that it is likely that transplantation is a cost-effective treatment option compared to dialysis,[13] with evidence from other European countries showing that this is very likely to be true.[14] A kidney transplant is not a 'cure' for the condition and there remain risks of failure for the grafted kidney after initial function.[10] In these cases, a patient may need to restart dialysis or can potentially receive a further kidney transplant. In order to minimise the risks of organ rejection, extensive tissue matching is undertaken to ensure a compatible kidney is used. Within the UK, there were 2339 adult kidney only transplants from a deceased donor in 2018/2019, a number that has been increasing by around 5% per year over the last 10 years.[15]

Some patients have an immunological barrier to transplantation in the form of antibodies directed against HLA antigens. HLAs are encoded by the major histocompatibility complex (MHC), which consists of more than 200 genes located on chromosome 6.[16] The genes of MHC include two classes that encode cell surface antigens, these are MHC class I and MHC class II.[16] Class I HLAs are present on almost all human cells (including all nucleated cells), and the three main genes are HLA-A, HLA-B, and HLA-C.[16] Class II HLAs are primarily expressed on antigen-presenting immune cells (such as B-cells, macrophages, and dendritic cells) and the major genes are HLA-DP, HLA-DQ, and HLA-DR.[16] Within these gene classes are a large number of individual HLA variants.[16]

These antibodies against HLAs arise through immunological sensitisation that can occur for a number of reasons.[17] The exposure of a potential recipient to allogeneic tissue bearing 'foreign' HLAs is the most common cause for sensitisation; such exposure can occur from transfusion of blood products, pregnancy (which includes miscarried and terminated pregnancies), or a previous transplant.[17] These HLA

reactive antibodies can also arise from cross-reactivity to pathogens (identified as idiopathic antibodies).[17] The antibodies may attack foreign tissue, such as the transplanted organ. Circulating anti-HLA antibodies specific to the HLA antigens of a potential donor organ, also known as donor specific antibodies (DSAs), are considered a barrier to transplantation as they can lead to immediate or hyperacute organ rejection. Some DSAs can be considered 'low risk' and these can be 'delisted' during the transplant matching process to remove them from consideration and potentially blocking a transplant. The complexity and variety in HLA types mean that organ matching requires expert clinical judgement to assess the patient-specific immunological profile.

Highly sensitised patients have antibodies to the majority of HLA present within donors. The degree of sensitisation is measured in the UK as the calculated reaction frequency (cRF).[18] The cRF is the percentage of 10,000 recent UK donors that the patient has pre-formed antibodies against and is measured when patients are listed for transplant.[19,20] A measure that is used commonly outside the UK is the calculated panel-reactive antibodies (cPRA), which is a computer-based method to test the reactivity of the patient's antibody profile against the HLA profile of >12,000 potential donors. There is no formally agreed definition for what constitutes being highly sensitised, but, most commonly, patients are considered to be highly sensitised if their HLA antibody profile reacts to ≥85% of donors (i.e cRF ≥85%).[21] The presence of DSA HLA antibodies to a large proportion of the donor pool means that finding a donor kidney is extremely difficult, if not impossible. The implication of this is that these highly sensitised patients are unlikely to receive a transplant or may face a substantially extended wait time for a compatible transplant. If no acceptable organ offer becomes available to these patients they will spend the rest of their life on dialysis with no other treatment options available to them.

Approximately 23% of patients on the kidney transplant waiting list in England are highly sensitised, with a cRF of ≥85%, which equates to over 800 highly sensitised patients (based on the kidney transplant list in England having around 3740 active adult patients in 2018/2019).[15,22,23]

B.1.3.2 Unmet need in highly sensitised patients

Highly sensitised patients face extended waits for a transplant, and therefore are likely to spend extended times on dialysis. The accrual of highly sensitised patients on wait lists is a growing problem in kidney transplantation; this is especially true as a longer time on the kidney transplant wait list has been shown to be independently associated with adverse outcomes before and after transplantation, especially for dialysis-dependent patients.[24] The updated UK kidney offering scheme (KOS), has been designed to try and address this problem of very long wait times for the most highly sensitised patients. Under the revised KOS, patients are categorised into Tier A or Tier B.[25] Tier A includes patients with a matchability score of 10, 100% cRF or ≥7 years waiting time. Tier B consists of all other patients prioritised by point scores based on a number of factors, namely: donor-recipient risk index combinations, waiting time, tissue match and age combined, location, matchability, total mismatch and blood group match.[25] On the UK transplant list, as of 31 March 2019, 6% of patients (298) have been waiting for a transplant for more than seven years, 98% of whom are highly sensitised with a cRF of 85% or higher. Of those waiting for more than seven years, 84% have a cRF of 100%.[15] This revised scheme has been in operation since only September 2019, and so its full impact cannot be reliably judged. However, it seems likely that even given this revised scheme that a group of patients will remain unlikely to receive a timely transplant and will experience extended wait times; this expectation was confirmed by UK clinical experts consulted by Hansa Biopharma AB. These patients who are unlikely to receive a transplant may experience deterioration in their condition whilst waiting for an acceptable kidney offer, such that they are no longer well enough to receive the transplant when one becomes available.

Kidney allocation schemes and acceptable mismatch programmes are used internationally to help expand the donor pool for highly sensitised patients, but despite these programmes, many highly sensitised patients remain on dialysis and never find a match.[26] This may consist of patients who are the most highly sensitised (cRF ≥99%), or those that are highly sensitised (cRF ≥85% and matchability scores of 8 or 9), but have a particular immunological profile that makes them unlikely to receive a transplant (e.g. high total mean fluorescence intensity [MFI]-load and/or a

number of problematic DSAs). Therefore, there remains a significant unmet need for these patients who remain unlikely to be able to receive a transplant despite the available prioritisation programmes for highly sensitised patients.

The only other current alternative therapies that may allow these patients to receive a transplant are desensitisation protocols. These off-label institutional desensitisation protocols are currently used at some hospitals; however, these mostly experimental protocols are neither standardised nor have regulatory approval.[27,28] If such a protocol would enable a crossmatch conversion in a timely manner, then it should be a preferred treatment option over imlifidase for those patients. However, these treatments may fail to achieve the required threshold of desensitisation in patients (especially within highly sensitised patients). In addition, these protocols need repeated dosing over several weeks or months before transplantation, which means that these protocols are only suitable for living donor transplants.[29] Therefore, these protocols do not offer a relevant clinical alternative to imlifidase. These treatments are also unlikely to significantly impact the transplant prospects of highly sensitised patients who are unlikely to receive a transplant within the UK, as there is no substantial use of these unlicensed desensitisation protocols within the UK.

Given the above, long-term dialysis represents the only alternative for potential imlifidase patients should they not be able to receive a transplant. Dialysis is the alternative form of RRT when transplant cannot occur. The two main modalities of dialysis are haemodialysis (HD) and peritoneal dialysis (PD). Dialysis is efficacious as a life-saving and extending treatment, but is also associated with a number of complications and a high burden on patients and caregivers. The main adverse events (AEs) associated with dialysis are: infection,[30] cardiovascular disease,[31] anaemia[31,32] and amyloidosis.[33] Over the long-term, these AEs are known to worsen and to become more burdensome to patients, with the risk of stroke being one example of an AE that accumulates over time on dialysis.[34] This leads to an increased mortality for patients on dialysis,[9] meaning that an inability to receive a transplant may translate into a reduced survival time for these patients on long-term dialysis. In addition, extended periods on dialysis may lead to vascular access problems over time as ports or venous access fail, which can create an urgent need for transplant.[30]

It is therefore not surprising that quality of life (QoL) has been shown to be lower for patients receiving dialysis compared to those who have received a transplant.[35] Quality of life can also decline over the long-term on dialysis due to adverse events and through the loss of hope of receiving a transplant (this can be seen to be particularly evident if the health of a patient declines and they are removed from the transplant list). This effect can be seen within data from a UK study which showed a small decrement in utility between patients who were predialysis, those who had <1 year of dialysis, those with 1–3 years of dialysis and those with >3 years of dialysis.[36] In addition, focussing on aspects of the patient experience highlights further the high burden from dialysis and the unpleasant AEs that can be experienced, which can be highly bothersome to patients. These AEs include sleep problems,[37] fatigue,[38] nausea,[38] muscle cramps,[38] itchiness,[38] weight gain,[30] and depression;[37] the NHS website lists the following additional AEs for dialysis:[39] hypotension, bone and joint pain, loss of libido, erectile dysfunction, dry mouth, and anxiety. Another factor around dialysis that can impose a high burden on patients is the time and travel requirements associated with dialysis. Standard in-centre HD (the most commonly utilised dialysis modality) typically requires a 3–4 hour session 3 to 4 times every week.[37] This time commitment and the associated travel time (travel costs are reimbursed by the NHS) severely impacts the lives of patients and their caregivers, and this includes impacting the professional life of a patient (leading to significant indirect costs that are outside the scope of NICE appraisals).[37] PD can also be associated with a high burden as the patient (and/or their caregiver) needs to schedule dialysis into their daily routine, set up and run home dialysis, which again is time-consuming and burdensome, and store the required supplies in their home.[37] The burdensome nature of dialysis means that it also has a negative impact on the ability of patients to work and their productivity (whilst this aspect falls outside the scope of NICE, it is an important factor for many patients).[40,41]

The negative impacts of extended dialysis are such that this can also be seen to be a risk factor for removal from the transplant wait list, as a result of the patients declining health whilst on dialysis. In the UK, after 1 year on the waiting list, 1% of patients were removed and 2% died.[15] After 3 years on the waiting list, 6% patients had been removed and 5% died.[15] In these highly sensitised patients, this means

that the delay in access to transplantation has the potential to mean a patient loses their opportunity to receive a transplant within the time window when they are able to receive it.

The combination of extended wait times for transplant and the negative impacts of extended dialysis result in a significant unmet medical need within these patients. In light of this, enabling transplant in highly sensitised patients by eliminating immunologic barriers is a significant advancement in therapy that acts to help meet this unmet medical need. To our knowledge, there are no other developments in the area of the indication, which again highlights that the management of highly sensitised patients remains an unmet clinical need.

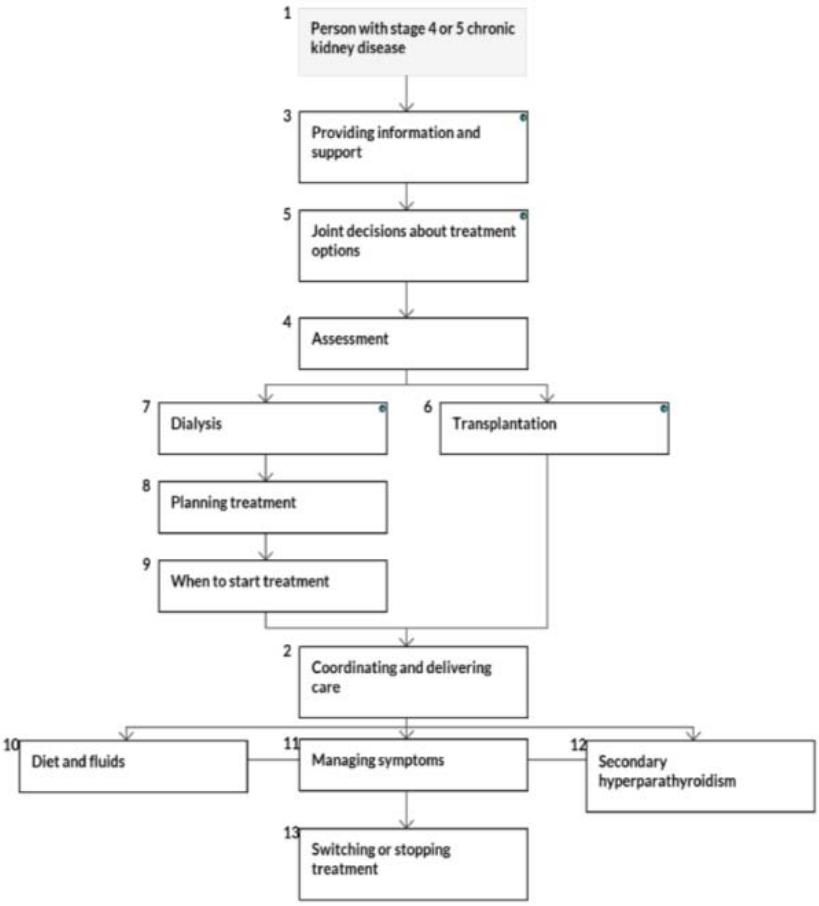
B.1.3.3 Clinical treatment pathway

As imlifidase is the first specific treatment option for highly sensitised patients, there is currently no defined NICE pathway for this patient group and no mention of sensitised patients within the NICE pathway for CKD.[13] The following NICE guidance and quality standards are relevant to CKD patients and therefore potentially relevant to this appraisal:

- NICE pathway for CKD[13]
- Chronic kidney disease in adults: assessment and management (CG182)[8]
- Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia (CG157)[42]
- COVID-19 rapid guideline: chronic kidney disease (NG176)[43]
- COVID-19 rapid guideline: renal transplantation (NG178)[44]
- Renal replacement therapy and conservative management (NG107)[45]
- Immunosuppressive therapy for kidney transplant in adults (TA481)[46]
- Machine perfusion systems and cold static storage of kidneys from deceased donors (NICE TA165)[47]
- Laparoscopic insertion of peritoneal dialysis catheter (NICE IPG208)[48]
- Robot-assisted kidney transplant (NICE IPG609)[49]
- Chronic kidney disease in adults (NICE QS5)[50]
- Renal replacement therapy services for adults (updated 2018). NICE quality standard 72.[51]

The most relevant guidance for the positioning of imlifidase is the CKD pathway section for RRT.[52] This pathway is replicated in Figure 1 and offers guidance on the treatment options available to these patients – dialysis or kidney transplantation.

Figure 1 NICE Pathway for renal replacement therapy



The proposed, revised pathway would include imlifidase as an option prior to transplantation (for relevant patients), with some implications on decisions regarding RRT. This broad positioning needs to be refined by defining the relevant patient group within prospective transplant patients.

The marketing authorisation of imlifidase indicates its use in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor.[3] The indication also contains a note that imlifidase should be reserved for patients unlikely to be transplanted under available kidney allocation systems including prioritisation programmes for highly sensitised patients.[3] For patients within the UK, this can be clearly interpreted to mean highly sensitised patients with a

positive crossmatch against a prospective deceased donor organ, who are unlikely to receive a transplant under the revised KOS. More specifically, it would be expected that highly sensitised patients would be broadly defined as those with a cRF ≥85%, in line with current UK practice.[21] Within this group of highly sensitised patients, imlifidase should be targeted at those who remain unlikely to be transplanted under the revised KOS. Identification of these patients will require the application of clinical judgement by healthcare professionals to the patient-specific immunological profile and the likelihood of the patient to receive a transplant.

Another aspect covered within the indication of imlifidase is the need for a positive crossmatch against the potential deceased donor organ. There are three main types of crossmatch test used within transplantation. The first of these is the complement dependent cytotoxicity (CDC) crossmatch test. This involves serum from the recipient being added to donor lymphocytes (T- or B-cell) in the presence of complement. A positive CDC crossmatch test occurs when DSAs bind to lymphocytes, activate complement and cause cell lysis (in over 20% of cells).[53] The second test type is fluorescence-activated cell sorting (FACS, also known as flow cytometry) crossmatch. This involves serum from the recipient being added to donor lymphocytes (T- or B-cell) in the presence of anti-IgG fluorescein-labelled antibodies. A positive test occurs when the anti-IgG fluorescein labelled antibodies bind to lymphocytes and are detected by flow cytometry. FACS is more sensitive than the CDC crossmatch and may be positive despite a negative CDC crossmatch due to detection of lesser levels of IgG HLA or non-HLA antibodies or a non-complement binding antibody.[53] The final test type is the virtual or predicted crossmatch. This involves serum from the recipient being added to synthetic beads with either a set of antigens or a single antigen. Each bead can be identified by an independent dye signature. Anti-HLA antibodies will bind to the specific bead and a detector antibody will then bind and sequester a reporter dye. A profile of the antibodies present in the recipient is built by checking beads for the reporter dye with a laser beam. This profile can be compared with the HLA construct of a potential donor thus predicting the result of crossmatch.[53] Within UK clinical practice, virtual crossmatch tests have become standard practice, with CDC crossmatch tests conducted as necessary. It is

therefore expected that imlifidase would be used in patients with a virtual positive crossmatch (or FACS positive, if conducted).

Clinical judgement is also needed around the risk profile of the transplant to ensure that the risk-benefit level is appropriate and clinically acceptable for the recipient. The British Transplant Society (BTS) guidelines include an assessment of immunological pre-transplant risk assessment based on donor crossmatch and antibody screening results.[54] These guidelines provide broad recommendations for classifying transplants into high, intermediate and standard risk.[54] These recommendations do not yet account for the use of imlifidase, and so are not directly applicable but outline how a number of factors can be used, combined with clinical judgement, to ensure that imlifidase is used in appropriate cases with an appropriate risk profile. For example, patients with T-cell CDC positive crossmatches, have previously shown to be high risk patients who often experience poor transplant outcomes.[53] As imlifidase reduces DSAs to allow transplant but does not provide a permanent elimination of DSAs, the long-term risk profile of the transplant requires balanced clinical judgement.

There are also considerations in regard to how imlifidase fits in relation to the KOS. UK expert clinical opinion, solicited by Hansa Biopharma AB, is that patients unlikely to be transplanted and, therefore, eligible for imlifidase can be found within both Tier A and Tier B of the KOS (patients in Tier B may be considered unlikely to be transplanted due, as an example, to the breadth and strength of the antibodies present against a wide range of HLAs). Expert opinion is that those patients unlikely to receive a transplant can be identified early in most cases (within two years of wait time). A timely assessment of ability to be transplanted avoids a seven year wait (one of the criteria for Tier A) that would lead to an avoidable prolonged period of dialysis likely to be detrimental to patient outcomes whilst increasing costs.

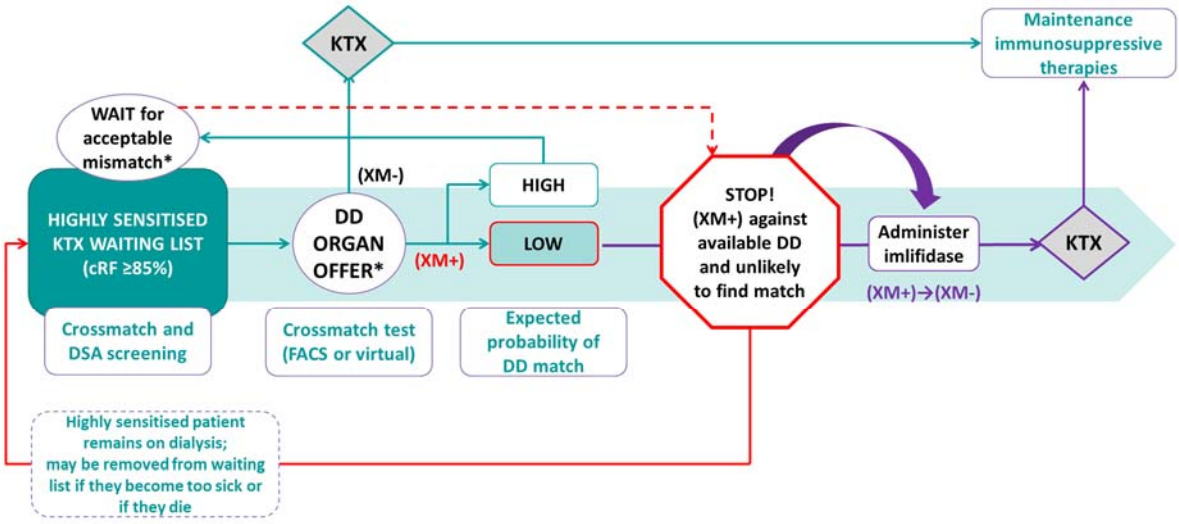
In summary, imlifidase should be available as a treatment option for adults with CKD awaiting a kidney transplant from an available deceased donor, if:

- The transplant recipient is highly sensitised (cRF ≥85%)
- There is positive crossmatch against the donor kidney

- The patient remains unlikely to be transplanted, despite the revised KOS (Tier A or Tier B)
- The transplant has an acceptable risk profile for the recipient.

This definition of imlifidase patients is also summarised diagrammatically within Figure 2. This schematic highlights how imlifidase is targeted at a small subgroup of patients eligible for kidney transplant, and hence that this is a highly specialised treatment that will be targeted at the unmet need in those patients who currently have very limited to no ability to receive a kidney transplant.

Figure 2 Schematic showing identification of imlifidase target patients



cRF: calculated reaction frequency; DD: deceased donor; DSA: donor specific antibody FACS: fluorescence-activated cell sorting; KTX: kidney transplant; XM-: crossmatch negative; XM+: crossmatch positive

Based on these definitions, the expected size of the patient group eligible for imlifidase is estimated to consist of around 113 patients in England. This equates to 13% of the 870 highly sensitised patients that are on the kidney transplant list. This estimate was based on clinical expert opinion gathered by Hansa Biopharma AB and through an informal survey of seven UK transplant centres who were asked to estimate the number of their patients that were expected to meet the criteria to be eligible for imlifidase. Further expert advice was sought to estimate how these patients divide between Tier A and Tier B of the KOS. It was estimated by clinical experts that around 10% of the transplant list corresponds to Tier A patients, and

that around 25% of these Tier A patients remain unlikely to be transplanted and hence eligible for imlifidase. This would correspond to 93 patients in Tier A and 20 patients in Tier B. This highlights that only small numbers of patients are expected to be eligible for imlifidase and most of these are within Tier A of the KOS. In addition, it must be remembered that these figures relate to numbers of eligible patients, and the numbers receiving imlifidase treatment will be further limited by the availability of donor kidneys (and the allocation of these kidneys within the KOS). Therefore, only a small proportion of imlifidase eligible patients would be expected to receive this treatment each year.

Hansa Biopharma AB expects that as a highly specialised treatment, imlifidase would be introduced using a centre-by-centre approach. The first centres and clinicians to use imlifidase are expected to be those that have expertise and experience in HLA incompatible transplantation, immunosuppressive therapies, and a detailed understanding of anti-HLA antibodies.

B.1.4 Equality considerations

People who are highly sensitised are currently not being provided the same access to kidney transplantation or standard of care as those whom are non-sensitised. This is evident in that the time on the waiting list for highly sensitised patients is over double that compared to non-sensitised patients, at over six years.[22] A cohort of highly sensitised patients are accumulating on transplant waiting lists; around 40% of patients waiting for a compatible kidney will not be transplanted within 5 years of being put on the waiting list.[19] The recent updates to the UK KOS provides evidence that there has historically been inequity between highly sensitised patients and non-sensitised patients, as the updated scheme now aims to better prioritise highly sensitised patients.[22,25] There remain particular groups where access to transplant is further restricted and where this inequality has not been resolved by the updated KOS.

B.1.4.1 Female population

Pregnancy is one of the most common causes for a patient to become sensitised with anti-HLA antibodies. Over a quarter of women develop anti-HLA antibodies after three or more pregnancies.[55,56] In addition, it has been documented that almost

three-quarters of women with a prior pregnancy become sensitised after a blood transfusion.[57] Due to this, there are a disproportionate number of women at the longer end of the waiting list spectrum (especially compared to the proportions entering onto the waiting list).[15] UKRR data show that the female gender is less likely to receive a deceased donor kidney transplant.[9] Women were 13% less likely to be added to the kidney transplant waiting list within 2 years of starting RRT compared to male counterparts (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.80–0.94). Once on the transplant waiting list, women were 16% less likely to receive a deceased donor kidney transplant within 2 years than men (OR 0.84, 95% CI 0.75–0.93).[9] The approval of imlifidase would provide an additional avenue for transplants and so can help equalise access to transplant for women.

B.1.4.2 Black, Asian and minority ethnic (BAME) populations

A recent comprehensive scoping review commissioned by Kidney Research UK found that ethnic minorities, although disproportionately represented in patient populations with ESKD, receive fewer transplants and wait longer to receive a transplant.[58] BAME groups represent 11% of the UK population; however, 31% of the kidney transplant waiting list was made up of BAME groups in 2019, which demonstrates a need for kidney transplant that exceeds that of white patients.[22,59,60] BAME patients experience waiting times 6 months longer than white patients, due to issues arising from the matching of blood and tissue types.[22,59,60] Data from UKRR show that patients of non-white ethnicity are significantly less likely to receive a deceased donor kidney transplant.[9] Once on the transplant waiting list, non-white patients had a 61% lower chance of receiving a deceased donor kidney transplant within 2 years (OR 0.39, 95% CI 0.35–0.44).[9] A previous analysis of UKRR data further supports this disparity. The likelihood of receiving a transplant from a donor after brain stem death within two years of registration on the waiting list was significantly reduced for those of non-white ethnicity (OR 0.47, 95% CI 0.37 to 0.59, P<0.001) compared with white ethnicity.[61] Those of non-white ethnicity were also less likely to receive a transplant from a donor after cardiac death or a living kidney donor within two years of registration on the waiting list (OR 0.57, 95% CI 0.46 to 0.7, P<0.001).[61] Additionally, a recent analysis of 1066 kidney transplant recipients (80 black patients, 986 white patients) within a single centre cohort (2007–2017) in

the UK found black patients had longer wait times, more difficult matchability (higher) scores and greater HLA-level mismatches compared with white patients.[62]

Whilst new allocation systems have reduced some racial/ethnic differences in obtaining a deceased donor transplant; for highly sensitised patients, this barrier to transplant still remains. Imlifidase offers highly sensitised BAME patients a desensitisation treatment option to enable access to a deceased donor kidney. These people with protected characteristics could gain more equitable access to a donor kidney sooner and, thus, are likely to have better outcomes once transplanted; therefore, addressing current inequalities.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

The efficacy of imlifidase has been evaluated in patients diagnosed with Stage 5 CKD awaiting kidney transplant in four Phase II studies. These studies were: 13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06. In addition, a follow-up study collecting long-term data on transplanted patients is ongoing (17-HMedIdeS-14, see Section B.2.11 for details).

The four Phase II studies that provide the key efficacy data in the clinical programme for imlifidase were all uncontrolled, open-label studies. The inability to conduct randomised controlled trials with imlifidase is due to a number of considerations around the nature of imlifidase treatment and the associated kidney transplant. It also reflects the targeted patient population of highly sensitised patients, which represents a small cohort of patients. Donor kidneys are a valuable resource with a highly restricted supply and the risk of an incompatible kidney transplant are well known.[18] There are a number of reasons for the use of an uncontrolled design in the trials; firstly, is the fact that there are no approved treatments for the desensitisation of patients who are highly sensitised. It would, therefore, be considered unethical, from a UK perspective, to conduct a randomised controlled trial for this treatment in these patients due to the lack of a safe and effective alternative therapy option to act as a comparator. Although off-label institutional desensitisation protocols are currently used at some hospitals, there is no consensus as to standard of care and these are mostly experimental treatments. These treatments also often fail to achieve the required threshold of desensitisation in patients, specifically within the necessary timeframe for deceased donor transplantation. As such, they are only used as a therapy option with living donors. A clinical study that would randomise patients to a known potentially unsuccessful desensitisation protocol was regarded as unethical and not feasible since it would inevitably risk the possibility for a patient

to be transplanted. Further, using an ineffective desensitisation protocol followed by transplantation would result in a high risk of graft rejection and associated complications. Another issue is that the heterogeneity of kidney allocation systems across countries makes it not possible to design and conduct a randomised controlled trial that reflects a population relevant to all countries.

Several publications have reported results from these Phase II trials (13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06), as summarised in Table 3.

Table 3 Published reports of imlifidase trials

Study	Published reports including results from study	Clinical trial registry numbers	Design
13-HMedIdeS-02	Jordan *et al.* 2017;[5] Lorant *et al.* 2018;[63] Lorant *et al.* 2016 (conference abstract);[64] Lorant *et al.* 2015 (conference abstract)[65]	NCT02224820, EudraCT 2013-005417-13	Open-label ascending-dose, Phase 2 study
13-HMedIdeS-03	Jordan *et al.* 2017;[5] Lorant *et al.* 2016 (conference abstract)[64]	NCT02475551, EudraCT 2014-000712-34	Open-label, single-group, Phase 1–2 study
14-HMedIdeS-04	Jordan *et al.* 2017;[5] Huang *et al.* 2019 (conference abstract);[66] Jordan *et al.* 2018 (conference abstract);[67] Jordan *et al.* 2017 (conference abstract);[68] Jordan *et al.* 2016 (conference abstract)[69]	NCT02426684	Open-label, single-group, Phase 1–2 study
15-HMedIdeS-06	Lonze *et al.* 2018[70]	NCT02790437, EudraCT 2016-002064-13	Open-label, single-group, Phase 2 study

The publication by Jordan *et al.* (2017)[5] is the main publication which covers analysis of transplanted patients from 13-HMedIdeS-02, 13-HMedIdeS-03 and 14-HMedIdeS-04. Lorant *et al.* (2018)[63] covers the results of trial 13-HMedIdeS-02, for the majority of patients who were not transplanted (this was primarily a dose finding study with an efficacy endpoint focussed on reaching acceptable criteria for a transplant). Lonze *et al.* (2018)[70] provides partial results from 15-HMedIdeS-06 focussed on the results from a single centre. The conference abstracts provide additional early reports on the results from these trials,[64,65,66,67,68,69] and the most recent abstract for 14-HMedIdeS-04 provides some data from additional longer term follow-up of these

patients.[66,67,68] A more formal long-term follow-up trial (17-HMedIdeS-14), covering all available transplanted patients, is currently ongoing (see Section B.2.11 for more details), but this study has not yet reported any formal results.

These studies used an adaptable definition of eligible patients based on local criteria where the studies were conducted. Therefore, an analysis of patients relevant to the expected licence and UK clinical practice will be presented within this submission as the primary population of interest. This sub-analysis will be conducted using a pooled patient group from across the clinical trials of imlifidase in order to maximise the size of this population (full details are within the meta-analysis section).

Table 4 Clinical effectiveness evidence – 13-HMedIdeS-02

Study	**13-HMedIdeS-02**				
Study design	Open-label ascending-dose study				
Population	Patients with chronic kidney disease with identified antibodies against at least two HLA antigens				
Intervention(s)	Imlifidase at 0.12mg/kg two doses, 0.25mg/kg one dose, 0.25mg/kg two doses				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	*X*	Indicate if trial used in the economic model	Yes	*X*
	No			No	
Rationale for use/non-use in the model	*Data from only transplanted patients in the study are included in the combined analysis used as a data source for the economic model*				
Reported outcomes specified in the decision problem	• Efficacy of imlifidase in reducing HLA antibody levels to a level acceptable for transplantation within 24 hours of dosing (measured as MFI of <1100 as measured in SAB assay) • Result in FACS crossmatch test against available donor cells after imlifidase treatment • Reduction of PRA levels in cytotoxic sera screen after imlifidase treatment • **Safety parameters (AEs, clinical laboratory tests, vital signs and ECG)**				
All other reported outcomes	• Pharmacokinetic profile of imlifidase • Pharmacodynamic profile of imlifidase (cleavage of IgG) • Immunogenicity of imlifidase (measuring anti-drug antibodies)				

AE: adverse event; ECG: electrocardiogram; FACS: fluorescence-activated cell sorting; HLA: human leukocyte antigen; IgG: immunoglobulin G; MFI: mean fluorescence intensity; PRA: panel reactive antibody; SAB: single antigen bead

Table 5 Clinical effectiveness evidence – 13-HMedIdeS-03

Study	**13-HMedIdeS-03**				
Study design	Open-label, single-group, Phase 1-2 study				
Population	Patients with chronic kidney disease intended for transplantation with at least one identified anti-HLA antibody ≥3000 MFI				
Intervention(s)	Imlifidase at 0.25mg/kg and 0.5mg/kg				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	*X*	Indicate if trial used in the economic model	Yes	*X*
	No			No	
Rationale for use/non-use in the model	*Data from the relevant transplanted patients are included in the combined analysis used as a data source for the economic model*				
Reported outcomes specified in the decision problem	• **Efficacy of imlifidase in reducing HLA antibody levels to a level acceptable for transplantation within 24 hours of dosing** • Result in FACS and CDC crossmatch test after imlifidase treatment • Reduction of PRA levels in cytotoxic sera screen after imlifidase treatment • Kidney function in patients transplanted • **Incidence of rejection, as well as patient and graft survival** • Time to recovery of total serum IgG and HLA antibody • **Safety parameters (AEs, clinical laboratory tests, vital signs and ECG)**				
All other reported outcomes	• Pharmacokinetic profile of imlifidase • Pharmacodynamic profile of imlifidase (cleavage of IgG) • Immunogenicity of imlifidase (measuring anti-drug antibodies)				

AE: adverse event; CDC: complement dependent cytotoxicity; ECG: electrocardiogram; FACS: fluorescence-activated cell sorting; HLA: human leukocyte antigen; IgG: immunoglobulin G; MFI: mean fluorescence intensity; PRA: panel reactive antibody

Table 6 Clinical effectiveness evidence – 14-HMedIdeS-04

Study	**14-HMedIdeS-04**				
Study design	Open-label, single-group, Phase 1-2 study				
Population	Highly sensitised chronic kidney disease patients awaiting kidney transplantation who had undergone prior desensitisation attempt(s) and have detectable DSA(s) or positive crossmatch tests				
Intervention(s)	Imlifidase at 0.24mg/kg				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	*X*	Indicate if trial used in the economic model	Yes	*X*
	No			No	
Rationale for use/non-use in the model	*Data from the relevant transplanted patients are included in the combined analysis used as a data source for the economic model*				
Reported outcomes specified in the decision problem	• **Number and levels of DSAs prior to and post transplantation (DSAs were defined as antibodies directed against donor HLA measured in SAB assay with MFI >2000)** • **Incidence of allograft rejection** • **Incidence of AMR findings at end of study** • Biopsy pathology evaluation • Renal function (creatinine, eGFR, and urine protein measurements) • Long-term allograft function (S-creatinine and eGFR) • **Safety parameters (AEs, laboratory assessments, vital signs, ECG)**				
All other reported outcomes	• Incidence of C4d depositions				

AMR: antibody-mediated rejection; AE: adverse event; DSA: donor specific antigens; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HLA: human leukocyte antigen; MFI: mean fluorescence intensity; SAB: single antigen bead

Table 7 Clinical effectiveness evidence – 15-HMedIdeS-06

Study	**15-HMedIdeS-06**				
Study design	Open-label, single-group, Phase 2 study				
Population	Kidney transplant patients who had previously undergone desensitisation unsuccessfully or in whom effective desensitisation would be highly unlikely				
Intervention(s)	Imlifidase at 0.25mg/kg (second dose if required)				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	*X*	Indicate if trial used in the economic model	Yes	*X*
	No			No	
Rationale for use/non-use in the model	*Data from the relevant transplanted patients are included in the combined analysis used as a data source for the economic model*				
Reported outcomes specified in the decision problem	• **Efficacy of imlifidase to create a negative crossmatch test within 24 hours after imlifidase dosing** • DSA levels pre- and post-imlifidase treatment • Kidney function (assessed by eGFR, creatinine and proteinuria) • **Safety parameters (AEs, clinical laboratory tests, vital signs and ECGs)**				
All other reported outcomes	• Time to negative CDC crossmatch test and negative FACS crossmatch test • Pharmacokinetic profile of imlifidase • Pharmacodynamic profile of imlifidase (cleavage of IgG) • Immunogenicity of imlifidase (measuring anti-drug antibodies)				

AE: adverse event; CDC: complement dependent cytotoxicity; DSA: donor specific antigens; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; FACS: fluorescence-activated cell sorting; IgG: immunoglobulin G

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial methodology

A summary of the main methodologies of the four clinical trials (13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06) are included in Table 8. As noted in the previous section of this submission, due to the nature of this treatment and the target patient population, there are no randomised controlled trials of imlifidase. Therefore, these four clinical trials are all open-label, single-group, Phase II (or Phase I/II) studies. The key design features of these trials, including key eligibility criteria, interventions used, and trial outcomes are all summarised in Table 8. Full details on inclusion and exclusion criteria are included within Appendix L of this submission.

Table 8 Summary of clinical effectiveness trial methods

Trial number	13-HMedIdeS-02	13-HMedIdeS-03	14-HMedIdeS-04	15-HMedIdeS-06
Location	Single centre in Sweden • Uppsala University Hospital	Two centres in Sweden • Uppsala University Hospital • Karolinska University Hospital	Single centre in USA • Cedars-Sinai Medical Centre	The study was conducted at five sites in three countries • Cedars-Sinai Medical Centre F, USA • The Johns Hopkins Hospital, USA • New York University School of Medicine, USA • Uppsala University Hospital, Sweden • Hôpital Necker, France
Trial design	Phase II, non-randomised, ascending dose study	Phase II, non-randomised, ascending single dose study	Phase I/II, non-randomised open label exploratory study	Phase II, single-arm, non-randomised, open-label study
Eligibility criteria for participants	**Key inclusion criteria** 1. Sign informed consent form (with ability to understand) 2. Aged 18 years or older 3. Diagnosis 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 4. Females of childbearing	**Key inclusion criteria** 1. Ability to understand and had signed the informed consent form 2. Age 18 years or above 3. Patients diagnosed with CKD and in dialysis with preformed anti-HLA antibodies (non-DSA, DSA or both), negative T-CDC crossmatch and at least one antibody MFI >3000 4. Available ABO-	**Key inclusion criteria** 1. ESRD awaiting transplantation on the UNOS list 2. Age 18–70 years at the time of screening 3. cPRA >50% demonstrated on 3 consecutive samples, patient highly-HLA sensitised and a candidate for deceased donor kidney transplantation after	**Key inclusion criteria** 1. Male or female aged 18–70 years at the time of screening 2. Patients on the kidney transplant waiting list who had previously undergone desensitisation unsuccessfully or in whom effective desensitisation or kidney paired donation was highly unlikely

	potential and males must use highly effective contraception during the study and at least for 12 weeks after discontinuation **Key exclusion criteria** 1. Tested positive for IgE antibodies against imlifidase 2. Prior malignancy within 5 years 3. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody or human immunodeficiency virus 4. Clinical signs of ongoing infectious disease 5. Severe other conditions requiring treatment and close monitoring 6. Previous treatment with biological antibody therapies (within 5 half-lives prior to imlifidase), rituximab/ cyclophosphamide (prior 6 months) 7. Participation in another clinical trial in previous 4	compatible donor (living or deceased donor) 5. Patients should be fit for surgery 6. Females of childbearing potential and males should use highly effective contraception during the study and at least for 12 weeks after discontinuation **Key exclusion criteria** 1. Prior malignancy within 5 years 2. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus 3. Clinical signs of ongoing infectious disease 4. Severe other conditions requiring treatment and close monitoring 5. Patients treated with biological therapies based on antibodies within at least 5 half-lives of that drug 6. Participated in any other clinical study that	desensitisation 4. At transplantation, the patient must have a DSA/crossmatch positive non-HLA identical donor 5. Able to understand and provide informed consent **Key exclusion criteria** 1. Use of IVIg within 7 days prior to planned imlifidase administration 2. Recipients of kidneys from Extended Criteria Donors or Living Donors 3. Women of child-bearing age who were not willing or able to practice Food and Drug Administration - approved forms of contraception 4. Positive test for hepatitis B or hepatitis C infection or human immunodeficiency virus 5. Selective IgA deficiency and those who have known anti-IgA antibodies 6. Use of investigational agents within 4 weeks of participation	In Sweden, additionally: a) Fulfil the criteria to be listed on the Scandia Transplant Acceptable Mismatch Program or on the Scandinavian Transplant Kidney Exchange Program In France, additionally: a) DSAs present b) MFI levels of at least 3000 3. Patients with a live or deceased (deceased donor not applicable in France) donor with a positive crossmatch test 4. Patients had to be able to understand and sign the informed consent **Key exclusion criteria** 1. Previous treatment with imlifidase 2. Previous high dose IVIg treatment (2 g/kg body weight) within 28 days prior to imlifidase treatment 3. Women of child-bearing age and men who were not willing or able to

	months	included drug treatment within previous 4 months		practice the required forms of contraception 4. Sweden: Patients tested positive for hepatitis B or hepatitis C infection France: Patients tested positive within for hepatitis B/C 1 year prior to enrolment USA: Patients with clinical signs of hepatitis B/C infection 5. Severe other conditions requiring treatment and close monitoring 6. Patients should not have received investigational drugs within 4 half-lives (or similar) 7. Patients who had a live donor and tested positive for ImmunoCAP anti-imlifidase IgE
Settings and locations where the data were collected	Data were collected during an initial 3-day residential period and at study visits over increasing time periods thereafter (days 4, 5, 7, 14, 21, 28 and 64); total follow-up period of 64 days	Data were collected during an initial 3-day residential period, an observation period (days 3–14) and during a follow-up period of 6 months	Data were collected during the treatment period (days 1–7), observation period (days 8–28) and during a follow-up period of 6 months	Data were collected during the treatment period (days 0–14), and during a follow-up period of 6 months

Trial drugs **Permitted and disallowed concomitant medication**	Intravenous imlifidase was administered over 15 minutes. Each patient received a single dose of imlifidase on Day 0. An additional second dose was administered within 2 days when considered necessary. The planned dose groups were: • 0.12mg/kg • 0.25mg/kg • 0.50mg/kg (optional) • 1.00mg/kg (optional) **Concomitant medications** Patients received premedication with methylprednisolone 250mg i.v. and 10mg loratadine p.o. before each imlifidase infusion (to minimise infusion reactions). All patients received prophylactic antibiotics, the first dose group received amoxicillin/ clavulanic acid tablets 500mg/125mg, this was replaced in second dose group with phenoxymethylpenicillin due to liver toxicity concerns in combination with tacrolimus;	Patients in the first dose group received one intravenous dose of 0.25mg/kg imlifidase over 15 minutes on Day 0. The second dose group received one dose of 0.50mg/kg after evaluation of the safety and efficacy in the first group. **Concomitant medications** Patients received premedication with methylprednisolone 250mg i.v. and 10mg loratadine p.o. before each imlifidase infusion. All patients received 1g phenoxymethylpenicillin once daily from the start of imlifidase treatment until recovery of serum IgG level (>3 g/L). The medication administered as standard of care of kidney transplant patients at the study sites were: • cefuroxime 1.5g i.v. immediately before transplantation • trimethoprin 80mg/ sulfamethoxazole 400mg	All subjects received a 15-minute intravenous infusion of imlifidase at a dose of 0.24mg/kg. **Concomitant medications** Premedication comprising methylprednisolone 40mg i.v., acetaminophen 650mg p.o. and diphenhydramine 150mg p.o. was administered. Patients also received prophylactic ciprofloxacin and alemtuzumab 30mg four days post-transplant. High dose corticosteroids were administered on days 1–4. Regardless of the cytomegalovirus status, patients received i.v. ganciclovir while inpatients and valganciclovir as outpatients for 6 months. Patients received fluconazole 100mg daily for one month and trimethoprim 80mg and sulfamethoxazole 400mg daily for 12 months. High dose IVIg (2g/kg) was administered on days 14–21 (Subject Nos. 401–414) or 7–14 (Subject Nos. 415–	Imlifidase was administered as an i.v. infusion over at least 15 minutes. The patients received a single dose of 0.25mg/kg imlifidase. If it was considered safe and the desired effect was not achieved (negative crossmatch test) after the first dose, an additional imlifidase infusion could be given within two days of the first infusion. **Concomitant medications** Patients received premedication with methylprednisolone, 250mg i.v. and loratadine 10mg p.o. or an equipotent antihistamine before each imlifidase infusion. All patients received prophylactic antibiotics or sulphonamides according to clinical practice at each site from the start of imlifidase treatment until the serum IgG level was back within normal range. Patients were treated with high dose IVIg 10% solution 2g/kg (maximum 140g for

	other alternatives were used if hypersensitive to beta-lactam antibiotics. Supportive therapy considered necessary for patient welfare was given at the discretion of the investigator and was recorded.	once daily • when tolerating oral treatment, or at discharge, all participants received valganciclovir 450mg daily Patients received the standard maintenance immunosuppression as at each site. Supportive therapy considered necessary for patient welfare was given at discretion of the investigator and was recorded.	417) after transplantation.	>70 kg) for 7 days after imlifidase treatment and 1g rituximab (anti-CD20 antibody) for 9 days after imlifidase treatment. Induction therapy could be used if indicated; either anti-thymocyte globulin or alemtuzumab. Patients were treated with immunosuppressing agents according to clinical practice at each study site. Supportive therapy considered necessary for the patient's welfare could be given at the discretion of the investigator and was recorded.
Primary outcomes	Efficacy, defined as the imlifidase dosing scheme resulting in HLA antibody levels which are acceptable for transplantation (measured as an MFI of less than 1100 as measured in a SAB assay, within 24 hours from dosing)	Safety parameters (AEs, clinical laboratory tests, vital signs and ECGs)	• Number and levels of DSAs prior to and post transplantation (DSAs defined as antibodies directed against donor HLA measured in the SAB-HLA assay with MFI value >2000) • Incidence of allograft rejections • Renal function (creatinine, eGFR, and urine protein	Efficacy, defined as imlifidase ability to create a negative crossmatch test within 24 hours after imlifidase dosing

			measurements) • Biopsy pathology evaluation • Safety parameters (AEs, laboratory assessments, vital signs, ECGs)	
Other outcomes used in the economic model/specified in the scope	• Reduction of PRA levels in cytotoxic sera screen after imlifidase treatment • Result in FACS crossmatch test against available donor cells after imlifidase treatment • Safety parameters (adverse events, clinical laboratory tests, vital signs and ECGs) • PK profile of imlifidase • PD profile of imlifidase (cleavage of IgG) • Immunogenicity of imlifidase (measuring ADA)	• Efficacy defined as the imlifidase dosing scheme resulting in HLA antibody levels acceptable for transplantation within 24 hours from dosing • Reduction of PRA levels in cytotoxic sera screen after imlifidase treatment • Result in FACS and CDC crossmatch test after imlifidase treatment • PK profile of imlifidase • PD profile of imlifidase (cleavage of IgG) • Immunogenicity of imlifidase by measuring ADA • Time to recovery of total serum IgG and HLA antibody • Kidney function in patients who were transplanted • The incidence of	• Incidence of AMR findings at end of study • Incidence of C4d depositions • Long-term allograft function (S-creatinine and eGFR)	• DSA levels at pre- and post-imlifidase treatment • Time to create a negative CDC crossmatch test (not applicable in France) • Time to create a negative FACS crossmatch test • Safety parameters (AEs, clinical laboratory tests, vital signs and ECGs) • Kidney function after imlifidase treatment assessed by eGFR, creatinine and proteinuria • PK profile of imlifidase up to day 14 • PD profile of imlifidase (cleavage and recovery of IgG) • Immunogenicity profile of imlifidase by measuring ADA

		rejection as well as patient and graft survival		
Pre-planned subgroups	None	None	None	None

AMR: antibody-mediated rejection; ADA: anti-drug antibody; AE: adverse event; CDC: complement dependent cytotoxicity; CKD: chronic kidney disease; cPRA: calculated panel reactive antibody; DSA: donor specific antigens; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; FACS: fluorescence-activated cell sorting; HLA: human leukocyte antigen; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IVIg: intravenous immunoglobulin; MFI: mean fluorescence intensity; PD: pharmacodynamic; PK: pharmacokinetic; p.o.: orally; PRA: panel reactive antibody; SAB: single antigen bead; UNOS: United Network for Organ Sharing

B.2.3.1.1 13-HMedIdeS-02

This study was designed as a dose escalation trial to find a dosing scheme for imlifidase that allowed the majority of patients to reach anti-HLA antibody levels that were acceptable for transplantation (primary objective). Patients received either 0.12 or 0.25mg/kg imlifidase. In all cases, imlifidase was given as an intravenous infusion over 15 minutes and each patient could be given an additional dose, as determined by the study investigator, based on both safety and efficacy criteria. The safety evaluation consisted of a review of safety laboratory results (clinical chemistry and haematology) and adverse events. If the safety evaluation was acceptable, and the desired efficacy criteria had not been achieved, an additional dose (at the same dose as the first) was given within 2 days of the first infusion. The efficacy requirements for this study were a decrease of MFI to less than 1100. Dosing was staggered so that there was a period of at least 7 days between patients in the same group. It was planned for two patients to be dosed in the first group, with two additional patients added to a group if it was deemed necessary in order to fully evaluate that dose. Dose escalation to a higher dose group was based on safety and efficacy evaluation of previous dose groups. The decision to proceed to a higher dose was evaluated by the Data Monitoring Committee (DMC) who decided whether it was safe to proceed to the next dose and if the dose should remain as outlined in the protocol or be adjusted. A gap of at least 14 days was set between the dosing of the first patient in the higher dose group and the last patient in the previous dose group. The final two dosing groups (0.50 and 1.00mg/kg) were optional, and to only be used if they were required to meet the efficacy aims of the study and provided that there were no major safety concerns at the lower doses.

The primary endpoint of this study was defined as imlifidase dosing resulting in anti-HLA antibody levels acceptable for transplantation (an MFI of less than 1100 measured in a single antigen bead [SAB] assay), within 24 hours after dosing. The SAB assay utilises an array of individual HLA (class I and class II) immobilised to solid-phase beads and allows a determination of the MFI of antibodies in patient serum reacting to each of these immobilised antibodies. The primary endpoint was assessed at baseline, and the following times post-baseline: 1 hour, 2 hours, 6 hours, 1 day, 7 days, 14 days, 4 weeks, and 9 weeks. In those patients requiring a

second dose of imlifidase, additional 1 hour, 2 hours, 6 hours, and 1 day assessments were completed.

Secondary outcomes were analysed in the following manner. For reduction of PRA levels in cytotoxic sera screen, samples were analysed for CDC against a panel of T- and B-cells to determine the PRA level; this was conducted at baseline, 1 hour, 2 hours, 6 hours, and 24 hours post-dose. For the FACS crossmatch test, samples were analysed for reactivity against lymphocytes from available donors using flow-cytometry to investigate the channel-shift (or MFI); this was conducted at baseline, 1 hour, 2 hours, 6 hours, and 24 hours post-dose. The pharmacokinetic profile of imlifidase was determined using venous blood samples (taken at baseline, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 24 hours, 48 hours, 72 hours, 7 days, 14 days, and 21 days post-dose) and were analysed using a validated electrochemiluminescence immunoassay. Pharmacokinetic calculations were performed using an open 2-compartment model (found to best describe the data). The pharmacodynamic profile of imlifidase cleavage of IgG was determined using venous blood samples (taken at baseline, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 24 hours, 48 hours, 72 hours, 7 days, 14 days, 21 days, 28 days, and 64 days post-dose), and were analysed using a validated enzyme-linked immunosorbent assay (ELISA). Anti-drug antibodies were determined using venous blood samples (taken at baseline, 24 hours, 5 days, 7 days, 14 days, 21 days, 28 days, and 64 days post-dose), and were analysed using an anti-IdeS ImmunoCAP method.

B.2.3.1.2 13-HMedIdeS-03

In this open-label, ascending single dose study, all patients received imlifidase infusion. The primary objective of this study was to assess the safety and tolerability of imlifidase, with the overall efficacy endpoint to find a dosing regimen that resulted in anti-HLA antibody levels which were acceptable for transplantation by means of a reduction of PRA levels and conversion to negative crossmatch tests. Patients were not randomised to dose groups, but were included in the dose group being investigated at the time of their treatment. Patients in the first dose group received one intravenous dose of 0.25mg/kg imlifidase over 15 minutes on Day 0. The second dose group received one intravenous dose of 0.50mg/kg over 15 minutes after

evaluation of the safety and efficacy in the first group. One or two optional higher dose groups were planned but were not dosed since it was considered not to be justifiable to escalate the dose above 0.5mg/kg for efficacy reasons. Dosing was staggered with at least 7 days between patients within a dose group. Furthermore, there was at least 14 days between dosing of the first patient in a higher dose group and dosing of the last patient in the previous dose group. The requirement for staggered dosing within a dose group was later removed since evaluation of safety data from 12 previously dosed patients showed that this was no longer necessary. The safety and efficacy were evaluated by the DMC before proceeding to a higher dose. After dosing of each group, the DMC decided if it was considered safe to proceed to the next dose group and if the dose in the next group should remain as planned or be adjusted to a lower dose level. Patients with living donors received imlifidase the day before transplantation, while patients with deceased donors received imlifidase on the day of transplantation. The infusion could be interrupted or slowed down, if required.

The primary endpoints of this study were safety parameters (AEs, clinical laboratory tests, vital signs and electrocardiograms [ECGs]). 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 considered causally related to the product or not. A serious AE (SAE) was defined as an AE occurring during any phase of the study that fulfilled one or more of the following criteria:

- resulted in death
- was immediately life-threatening
- required in-patient hospitalisation or prolongation of existing hospitalisation (regular dialysis treatment in or outside hospital and hospitalisation for transplantation were not included)
- resulted in persistent or significant disability or incapacity
- was a congenital abnormality or birth defect
- was an important medical event that could jeopardise the patient or could require medical intervention to prevent one of the outcomes listed above.

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "*Have you had any health problems since you were last asked?*" or revealed by observation were collected and recorded. Laboratory values, vital signs and other safety variables were reported as AEs if they were deemed clinically significant or if they required medical treatment. The investigator was responsible for collecting AEs from the time of admission to the Section of Transplant Surgery (Day -1) and throughout the study including the follow-up period (until Day 180 ± 7 days).

The following information was collected for all AEs and recorded:

- description of the AE
- duration (start and stop date and time)
- Common Toxicity Criteria for Adverse Events (CTCAE) grade (according to CTCAE v.4.04)
- seriousness (did the AE meet any SAE criteria, yes/no)
- causal relationship to imlifidase (not related, unlikely, possible or probable)
- action taken with regard to imlifidase (none, medical treatment, withdrawn, other)
- outcome (resolved, resolved with sequelae, not recovered/ongoing).

Blood samples for determination of clinical chemistry, haematology, coagulation, serology and complement function screening were taken at: baseline, pre-dose, 24 and 72 hours, and on days 4, 5, 7, 14, 21, 28, 64, 90 120, 150, and 180 (6 months). Vital signs (blood pressure, pulse and respiratory frequency) were measured at the following time points: baseline, pre-dose, 15 minutes, 1, 2, 6 and 48 hours and then on days 7, 28, 90 120, 150, and 180 (6 months). ECGs were listed in the protocol as part of the DMC safety data package, but only recorded after 10 minutes rest at screening and on Day 180.

Secondary endpoints were analysed as follows. Efficacy was defined as imlifidase dosing resulting in anti-HLA antibody levels acceptable for transplantation (an MFI of less than 1100 measured in a SAB assay) within 24 hours after dosing. This endpoint was assessed at: baseline, pre-dose, 1, 2, 6, 24 hours, and then days 7, 14, 28, 64, and 180. This assay also provided data for the endpoint assessing the recovery of anti-HLA antibodies. To assess reduction of PRA levels in cytotoxic sera

screen, blood samples were analysed for CDC against a panel of T- and B-cells pre- and post-treatment with imlifidase. This endpoint was assessed at: baseline, pre-dose, 1, 2, 6, 24 hours. For FACS crossmatch test, samples were analysed for reactivity against lymphocytes from their organ donors to investigate if the crossmatch test was positive or negative based on the channel-shift (or MFI) determined by flow-cytometry. In agreement with clinical practice, the FACS crossmatch tests were only performed pre-dose and once post-dose and not at pre-dose and at 1, 2, 6, and 24 hours post-dose as stated in the original protocol. A CDC crossmatch test was performed at screening for all patients as part of the inclusion criteria check.

The pharmacokinetics (PK) profile of imlifidase was analysed by an electrochemiluminescence assay from blood samples taken at pre-dose, 15, and 30 minutes, 1, 2, 4, 6, 8, 24, 48, 72 hours, and days 4, 5, 7, 14 and 21. Pharmacokinetic calculations were performed using an open two-compartment model (found to best describe the data). The pharmacodynamics of imlifidase (IgG cleavage and processing) were investigated using three different methods; a total p-IgG turbidimetric assay, an electrochemiluminescence method to determine IgG in serum and a qualitative sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE) analysis. Blood samples were taken at pre-dose, 15 and 30 minutes, 1, 2, 4, 6, 8, 24, 48, 72 hours, and days 7, 14 and 21 (additional samples at 28 and 64 days for SDS-PAGE only). Recovery of IgG was based on analyses of the safety samples using a turbidimetric assay, since these were collected until Day 180 (baseline, pre-dose, 24, and 72 hours, and on days 4, 5, 7, 14, 21, 28, 64, 90, 120, 150, and 180). Kidney function was evaluated by the following parameters: creatinine, estimated glomerular filtration rate (eGFR) and kidney biopsy findings. Blood samples were taken at baseline, pre-dose, 24 and 72 hours, and on days 4, 5, 7, 14, 21, 28, 64, 90, 120, 150, and 180 (6 months). Histopathology was performed according to the protocol by kidney biopsies taken at 2 weeks (optional) and 6 months.

This inclusion protocol of the study was amended before the first patient was enrolled. Inclusion criterion number 3 was changed to the following, "*Patients diagnosed with CKD and in dialysis with preformed anti-HLA antibodies (non-DSA, DSA or both), negative T-CDC crossmatch and at least one antibody MFI >3000*".

This change was made to allow for the inclusion of patients who were more highly sensitised, based on the preliminary data in a Phase II study ongoing at the time, which showed a high efficacy within patients (including those who were highly sensitised). An exclusion criterion was added during the course of the study, which was "*Known horse allergy*"; this was added as horse-derived anti-lymphocyte immunoglobulin was to be used for high risk patients to prevent antibody-mediated rejection (AMR). All other protocol amendments were administrative or clarifications, with the following major exceptions. During the course of the study, the requirement for doses within a dose group to be staggered by at least seven days was removed (the 14 day gap between dose escalation was retained). This was done as the safety data gathered by that point in the study suggested that this staggering was no longer required. The number of patients in each dose group was also amended during the study; this was based on the results of 13-HMedIdeS-02 which showed that the higher doses planned in this study were not necessary. Therefore, the protocol was amended to include more patients in the lower dosing groups (a minimum of two patients and up to eight per dosing group).

B.2.3.1.3 14-HMedIdeS-04

This was a Phase II, single centre, uncontrolled, single dose, investigator-initiated study including 17 highly sensitised patients diagnosed with CKD receiving an intravenous infusion of 0.24mg/kg imlifidase over 15 minutes, administered 4–6 hours prior to transplantation.

The primary objective was to assess the efficacy of imlifidase in eliminating DSA in highly sensitised patients prior to transplantation. Secondary objectives were to assess the prevention or significant reduction in AMR episodes and C4d deposition, and to assess allograft function up to 6 months post transplantation. There were several primary endpoints in this study, which were analysed in the following manner. DSAs were 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. HLA-SAB results from the site's local transplantation laboratory were used for matching of donor-recipient. For the primary endpoint anti-HLA levels and DSA levels and for calculating the HLA-SAB MFI values, data from a central laboratory evaluation were used. DSA levels

were recorded at transplant (Day 0), 2 and 6-hours post-transplant and then on days 1, 2, 3, 4, 7, 14, 30, 90, and 180. The incidence of allograft rejections were recorded throughout the study. Kidney function as assessed by creatinine, eGFR and urinalysis (urine protein) was recorded at baseline, transplant (Day 0), day 1, 2, 3, 4, 5, 7, 14, 21, 30, 90, and 180. A protocol biopsy for evaluation of the kidney status was scheduled at the last visit, Day 180. If evidence of allograft dysfunction occurred, a non-protocol biopsy for cause was performed.

In terms of analysing safety parameters, 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 considered causally related to the product or not. A pre-treatment AE was any untoward medical occurrence arising or observed between signing the informed consent form and administration of study medication. A SAE was any untoward medical occurrence or effect that at any dose:

- resulted in death
- was life-threatening
- required in-patient hospitalisation or caused prolongation of existing hospitalisation (at least 24 hours excluding regular dialysis treatment in or outside hospital and hospitalisation for transplantation)
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect; observed in any offspring of the subject conceived during treatment with imlifidase
- was an important medical event that might have jeopardised the patient or required intervention to prevent one of the other outcomes listed in the definition above
- any suspected transmission of an infectious agent via a medicinal product.

The investigator monitored the condition of the subject throughout the trial from the time of obtaining informed consent until the end-of-trial visit or end of follow-up period, as applicable. Collection of AEs comprised the subject's positive response to questions about their health, symptoms spontaneously reported by the subject, and clinically relevant changes and abnormalities observed by the investigator. Laboratory values, vital signs and other safety variables were reported as AEs if they

were deemed clinically significant or if they required medical treatment. The following information was collected for all AEs:

- description of the AE
- duration (start and stop date and time)
- CTCAE grade (according to CTCAE v.4.04)
- seriousness (did the AE meet any SAE criteria, yes/no)
- causal relationship to imlifidase (not related, unlikely, possible or probable)
- action taken with regard to imlifidase (none, medical treatment, withdrawn, other)
- outcome including date and time (resolved, resolved with sequelae, not recovered/ongoing)

Blood samples for determination of clinical chemistry, haematology, coagulation, complement function screening were analysed using routine methods. They were measured at the same time points as the vital signs (blood pressure, pulse and respiratory frequency): baseline, transplant (Day 0), days 1, 2, 3, 4, 5, 7, 14, 21, 30, 90, and 180. A 12-lead ECG was recorded after 10 minutes rest at screening and on Day 180.

Secondary endpoints were analysed as follows. A protocol biopsy was performed to assess the allograft for signs of AMR, including C4d staining, after 6 months. AMR was defined according to the Banff 2017 criteria.[71] The long-term function of the kidney was assessed 6 months after imlifidase treatment by means of serum creatinine and eGFR.

The exclusion criteria of this study were amended after a single enrolment had occurred. The use of intravenous immunoglobulin (IVIg) was amended to within seven days prior to imlifidase (amended from four weeks) and a positive test for hepatitis B virus (HBV) or hepatitis C virus (HCV) was added. A further change was made during the course of the study which removed the requirement for a negative anti-imlifidase immunoglobulin E (IgE) test (as such a result was considered highly unlikely). All other changes to the protocol were administrative. The one exception was that the planned dosing increase to 0.5mg/ml was cancelled during the course of the study.

B.2.3.1.4 15-HMedIdeS-06

This was a multi-centre, uncontrolled study in which imlifidase was administered as an intravenous infusion over at least 15 minutes using a syringe or an infusion bag, an infusion pump and a particle filter. Patients received one dose of 0.25mg/kg imlifidase on Day 0. If it was considered safe and the desired effect was not achieved (negative crossmatch test) after the first dose (primary objective), an additional imlifidase infusion (0.25mg/kg) could be given within two days of the first infusion.

The primary endpoint was efficacy defined as imlifidase ability to create a negative crossmatch test within 24 hours after imlifidase dosing. CDC and FACS crossmatch tests were performed at pre-dose and 2, 6, and 24 hours post-dose. The pre-dose analyses were performed for all patients, while all post-dose crossmatch 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 crossmatch tests were performed. Crossmatch tests were performed at the local laboratories according to standard practice at each local laboratory. Time to creating a negative CDC crossmatch test (not applicable in France) and a negative FACS crossmatch test were recorded as secondary endpoints.

The remaining secondary endpoints were analysed in the following way. Samples for determination of DSAs were analysed in SAB solid-phase assay for antibodies to HLA class I and class II. DSA levels were recorded at baseline, pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120, and 180 post-imlifidase.

Safety parameters (AEs, clinical laboratory tests, vital signs and ECG) were assessed as secondary endpoints in the study. Data on AEs were obtained if spontaneously reported by the patient, if reported in response to an open question from the study personnel, or if revealed by observation. AEs were collected from the time of signing of the informed consent and throughout the study, including the follow-up period. 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 considered causally related to the product or not. The intensity of AEs was graded according to CTCAE v.4.03.

Blood samples for determination of clinical chemistry, haematology, coagulation and serology were collected at baseline, pre-dose, 2, 6, 24, and 48 hours post-dose, and then days 7, 14, 21, 28, 64, 90, 120, and 180 and analysed at local laboratories using routine methods. Vital signs (blood pressure, pulse, respiratory frequency) were recorded at baseline, pre-dose, 2, 6, 24, and 48 hours post-dose, and then days 7, 28, 90, 120, and 180. A 12-lead ECG was measured after 10 minutes rest at screening and Day 180 and assessed as normal, abnormal not clinically significant or abnormal clinically significant.

Evaluation of kidney function was performed based on p-creatinine analysis and calculation of the eGFR at 24 and 48 hours post-dose, and on days 14, 21, 28, 64, 90, 120, and 180. Proteinuria tests (spot urine/creatinine) were performed at day 14, 28, 64, 90, 120, and 180. In addition, 24-hour urine collections were performed daily from the time of transplantation to Day 9, for determination of 24-hour urine volumes and electrophoresis analysis of protein, which were performed at the local laboratories. However, since the electrophoresis analyses did not provide the information required to meet the objective of the study, the urine samples were also analysed using SDS-PAGE/Western blot.

Samples for determination of imlifidase levels in serum (PK profile) were collected at pre-dose, 2, 6, 24, and 48 hours post-dose, and then on days 3, 6, 7, 9, and 14. Analysis was by an electrochemiluminescent immunoassay. Standard PK parameters were derived to describe the PK profile of imlifidase. Samples for determination of IgG levels in serum (pharmacodynamic profile of imlifidase) were collected at pre-dose, 2, 6, 24, and 48 hours post-dose, and on days 7, 9, 14, 21, 28, 64, and 180. Intact IgG and scIgG serum concentrations were analysed using an electrochemiluminescent immune assay. Furthermore, samples were qualitatively analysed by gel electrophoresis for IgG integrity. Blood samples for determination of anti-drug antibodies were collected pre-dose and 48 hours post-dose, and then on days 7, 14, 21, 28, 64, 90, 120, and 180. Analyses were performed using a customised ImmunoCAP.

During the course of the study the following amendments were made to inclusion and exclusion criteria:

- For the second inclusion criterion (CKD patients and previous desensitisation) country specific criteria were added
- Acceptable contraception according to EMA guidelines were added to relevant exclusion criterion
- Exclusion criterion around known allergy/sensitivity to imlifidase infusions was changed to known allergy/sensitivity to any of the ingredients of the investigational medical product
- Third inclusion criteria (live/deceased donors) was amended to clarify that deceased donor was not applicable in France
- Exclusion criteria on contraception was modified to add that in France an exclusion was included of "*Men who were not willing to use double-barrier contraception from the first day of treatment until at least 14 days after the last dose of treatment*"
- Exclusion criterion of "*Patients with a history of clinically significant thrombotic episodes and patients with active peripheral vascular disease*" was changed to "*Patients with a history of major thrombotic events, patients with active peripheral vascular disease or patients with proven hypercoagulable conditions*"
- Exclusion criterion on HBV/HCV infection was modified in USA to "*Patients with clinical signs of HBV or HCV infection*", and in France "*within one year prior to enrolment*" was added
- Exclusion criterion on active cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection was modified in USA to "*Patients with clinical signs of CMV or EBV infection*", and in France "*with or without a compatible illness*" was added.

The finalised inclusion and exclusion criteria are those reported in the above section.

B.2.3.2 Patient baseline characteristics

The baseline characteristics of the participants in each trial are summarised in the following sections.

B.2.3.2.1 13-HMedIdeS-02

Table 9 Baseline characteristics of patients in 13-HMedIdeS-02

		Dose group 1 (n=3)	Dose group 2 (n=4)	Total (n=8)*
Age	**Mean (SD)**	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	48.5
	Range	[redacted]	[redacted]	31–69
Sex, n (%)	**Female**	[redacted]	[redacted]	5 (62.5%)
	Male	[redacted]	[redacted]	3 (37.5%)
Race, n (%)	**Caucasian**	[redacted]	[redacted]	[redacted]
Height (cm)	**Mean (SD)**	[redacted]	[redacted]	[redacted]
	Range	[redacted]	[redacted]	[redacted]
Weight (kg)	**Mean (SD)**	[redacted]	[redacted]	[redacted]
	Range	[redacted]	[redacted]	[redacted]
Body mass index	**Mean (SD)**	[redacted]	[redacted]	[redacted]
	Range	[redacted]	[redacted]	[redacted]

*1 patient had dose interrupted and so is included in total but not individual dose groups. SD: standard deviation

B.2.3.2.2 13-HMedIdeS-03

Table 10 Baseline characteristics of patients in 13-HMedIdeS-03

		Total (n=10)
Age	**Mean (SD)**	51.6 [redacted]
	Range	[redacted]
Sex, n (%)	**Female**	7 (70.0%)
	Male	3 (30.0%)
Race, n (%)	**Caucasian**	9 (90.0%)
	Asian	1 (10.0%)
Height (cm)	**Mean (SD)**	[redacted]
	Range	[redacted]
Weight (kg)	**Mean (SD)**	[redacted]
	Range	[redacted]
Body mass index	**Mean (SD)**	[redacted]
	Range	[redacted]

SD: standard deviation

B.2.3.2.3 14-HMedIdeS-04

Table 11 Baseline characteristics of patients in 14-HMedIdeS-04

		Total (n=17)
Age (years)	**Mean (SD)**	41.3 (13.3)
	Median	41
	Range	20–63
Sex, n (%)	**Female**	9 (52.9%)
	Male	8 (47.1%)
Race, n (%)	**Caucasian**	14 (82.0%)
Weight (kg)	**Mean (SD)**	65.5 (18.0)
	Median	68.8
	Range	31.3–94.6
Body mass index	**Mean (SD)**	24.4 (5.5)
	Median	24.3
	Range	13.5–36.6

SD: standard deviation

B.2.3.2.4 15-HMedIdeS-06

Table 12 Baseline characteristics of patients in 15-HMedIdeS-06

		Total (n=19)
Age (years)	**Mean (SD)**	39.1 (10.8)
	Median	40
	Range	20–64
Sex, n (%)	**Female**	6 (31.5%)
	Male	13 (68.4%)
Race, n (%)	**Asian**	1 (5.3%)
	Black or African American	4 (21.1%)
	White	12 (63.2%)
	Other	2 (11.5%)
Weight (kg)	**Mean (SD)**	73.2 (15.7)
	Median	71.6
	Range	45.1–107.4
Body mass index (kg/m^2)	**Mean (SD)**	24.6 (4.5)
	Median	24.3
	Range	17.5–32.5

SD: standard deviation

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Appendix D gives the patient flows through all of the clinical trials reported here.

All of these studies are non-randomised and non-controlled and therefore are at a risk of bias. There are no known and obvious factors that would lead to a bias within the primary endpoint of these studies (ability of imlifidase to decrease levels of anti-HLA antibodies within 24 hours to make the patient eligible for kidney transplantation). This was confirmed by discussion with clinical experts and was considered at all stages throughout the clinical trial process.

B.2.4.1 13-HMedIdeS-02

Within this trial, the following three analysis sets were used. The safety set included all patients that received any amount of study medication; this set was used for the baseline characteristics and safety data. The per-protocol set (PPS) consisted of all patients who received at least one dose of imlifidase and had evaluable pharmacokinetic data as determined by the study pharmacokineticist. All patients except one (whose dosing was interrupted) were included in the PPS. The pharmacokinetic and pharmacodynamic data in this study were based on the PPS. The Full Analysis Set (FAS) consisted of all patients that received any amount of study medication and had a measurement of anti-HLA antibody level within 24 hours from dosing. All efficacy data were based on the FAS, with the following exceptions: study investigators decided that one patient (dose interrupted) should be excluded from the analysis of C1q and B-cell receptor; and that one additional patient should be excluded from the C1q analysis (high background reading). Available data from prematurely withdrawn subjects was included in the analyses as far as possible and no imputation of missing data was undertaken in this study.

Due to the nature and design of this study, the sample size was not based on formal statistical considerations. Based on the nature of the primary endpoint, it was expected that data from four patients would suffice to achieve the objectives of the study (which is in line with other, previous, similar Phase II studies).

The analysis of the primary endpoint in this study determined efficacy as the ability of imlifidase treatment to lower anti-HLA antibody levels to those which are acceptable for transplantation (measured as an MFI of less than 1100 in a SAB assay), within 24 hours from dosing. In these SAB assays, approximately 200 different HLA values per patient and time point are produced. Those values that were above a level of 1100 at pre-dose measurement were selected and then these values were monitored after dosing. Summary statistics for each patient with selected HLA values were produced, but no statistical analysis was undertaken.

There was no interim analysis for this study, and there were no pre-defined subgroup analyses.

B.2.4.2 13-HMedIdeS-03

Within this trial, the following three analysis sets were used. The Safety Analysis Set (SAS) consisted of all patients who received any amount of study medication; this set was used to evaluate safety parameters which were presented by dose group and for the total population. All baseline and demographic data were presented for the SAS. 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. The PPS was defined by the pharmacokinetic analyst and was also called the pharmacokinetic analysis set. The final criteria for the pharmacokinetic analysis set regarding which protocol deviations necessitated exclusions was determined when all data on protocol deviations were available. All PK and pharmacodynamic data were presented for the PPS. No patients withdrew from the study or were excluded from efficacy analyses and no imputation of missing data was undertaken.

The nature and design of this study meant the sample size was not based on formal statistical considerations. Due to the nature of the primary endpoints, it was expected that data from four patients would suffice to achieve the objectives of the study (which is in line with other, previous, similar Phase II studies).

The analysis of the primary endpoints (AEs, clinical laboratory tests, vital signs and ECGs) involved only descriptive statistics. AEs were classified according to Medical

Dictionary for Regulatory Activities (MedDRA) version 18.1. Any AE with a start time before treatment start was defined as pre-treatment while all AEs occurring after the start of treatment were categorised as treatment emergent. A treatment-emergent AE overview summary table was prepared. The safety laboratory parameters were tabulated by time point. The other safety parameters (vital signs, body temperature, peripheral oxygen saturation, ECG and physical examination) were tabulated by time point.

Interim study data was reviewed by an independent DMC who advised on the progression of dosing from one dose level of imlifidase to the next. The DMC reviewed and evaluated safety and tolerability data. If a dose-limiting toxicity (DLT - any novel AE with a CTCAE grade 3 or more and with a possible relationship to imlifidase) was demonstrated in a patient at any dose level, the dose group should be reinforced to a total of at least 3 patients. If a DLT was demonstrated in 2 patients or more, the dose escalation was to be stopped or adjusted. A well-tolerated lower dose could be repeated or an intermediate dose could be given in another group of patients, if considered safe by the DMC.

This study undertook no interim analysis, and there were no pre-defined subgroup analyses.

B.2.4.3 14-HMedIdeS-04

Within this trial, the following two analysis sets were used. The SAS comprised data from all dosed subjects and was analysed according to the actual treatment received. Descriptive statistics of demographic and other baseline characteristics are presented for the SAS. The FAS consisted of all patients in the SAS that had recorded at least one efficacy endpoint value. The number of subjects screened, but not dosed, was stated but otherwise not accounted for. Missing data were not imputed or adjusted for in other ways.

Due to the nature and design of this study, no formal sample size calculation was performed for this Phase I/II study. Approximately 20 subjects receiving active treatment was considered sufficient to provide adequate information for the purposes of this study.

There were several primary endpoints analysed in this study. The SAB-HLA was summarised by patient and time point and presented as listings. Positive SAB-HLA were defined as having pre-dose levels above 3000 MFI. The positive SAB-HLA were summarised and presented in box-plots. The DSA were summarised by patient and time point and shown as listings. DSA were presented graphically as scatter plots (MFI versus time) with one separate plot for each patient and each DSA with a separate symbol but with no connecting lines. Dates of allograft biopsies both pre-transplantation, during study, and at day 180 were listed. Delayed graft function (DGF) was listed. Graft rejection episodes were listed.

The kidney function after imlifidase was assessed by filtration (eGFR), creatinine and proteinuria up to 180 days post-treatment. Each variable was tabulated by time point. The eGFR was calculated as:

eGFR (mL/min/1.73m2) = 175 × (Scr) – 1.154 × (Age) – 0.203 × (0.742 if female) × (1.212 if African American), where Scr stands for creatinine value in serum.

AEs were classified according to MedDRA version 18.1. A treatment emergent AE was any AE occurring after the administration of imlifidase and within the time of the residual effect period, or a pre-treatment AE or pre-existing medical condition that worsened in intensity after administration of imlifidase and within the time of the follow-up period. Based on the half-life and the pharmacodynamic properties of imlifidase the residual drug effect was considered 30 days after administration. An AE overview summary table was prepared. Clinical laboratory tests were summary tabulated. Vital signs and ECGs were summary tabulated.

This study undertook no interim analysis, and there were no pre-defined subgroup analyses.

B.2.4.4 15-HMedIdeS-06

Within this trial, the following three analysis sets were used. The SAS comprised data from all patients dosed with any amount of study medication. Demographics and other baseline characteristics were presented for the SAS group. The FAS comprised data from all patients in the SAS with available post-dose efficacy data. The FAS was used for presentation of efficacy endpoints. The PPS consisted of all

patients in the safety set who had at least one efficacy endpoint value. Data from patients with one or more major protocol deviations were excluded. The PPS was used for presentation of PK and pharmacodynamic endpoints. Missing data were in general not imputed or adjusted for in other ways.

Due to the nature and design of this study, no formal sample size calculation was performed for this study. Based on the nature of the primary endpoint of the study, it was expected that data from 15 to 20 patients should suffice to achieve the objectives of the study.

The analysis of the primary endpoint in this study was defined as imlifidase ability to create a negative crossmatch test within 24 hours after imlifidase dosing. The planned time points were: Screening, pre-dose, 2, 6, 24, and 48 hours. In general, only the pre-dose and 24 hour analyses were performed, while the other planned analyses were missing. For each of the crossmatch tests (FACS B-cell, FACS T-cell, amplified and non-amplified analyses of CDC B-cells and CDC T-cells, and virtual) summary tabulations by time point were made. For each patient, an overall response was defined as positive if at least one of the assays was positive at pre-dose and all recorded assays were negative at 24 hours. The overall response was summary tabulated.

This study undertook no interim analysis, and there were no pre-defined subgroup analyses.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The clinical studies that provide the key clinical evidence for imlifidase were all uncontrolled, open-label studies. This raises well-known potential limitations in the quality of these studies. The trials for imlifidase were designed in the most robust way possible in order to minimise any quality implications from their non-randomised and non-controlled design. The trials were conducted using this design as there was an inability to conduct randomised controlled trials due to a number of reasons, as outlined in previous sections. This was primarily due to the nature of imlifidase treatment and the fact that it was not considered ethical to undertake any randomised controlled trials due the lack of a suitable, safe, and effective comparator.

The quality of these studies was assessed using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool.[72] This tool was designed for assessment of the risk of bias in non-randomised studies, and is recommended by the Cochrane Handbook.[73] ROBINS-I shares many features of assessment with the Cochrane Risk of Bias tool for use in randomised trials but has been adapted to be appropriate for use with non-randomised studies. A full assessment of the identified studies of imlifidase using ROBINS-I is included in Appendix D, and a summary of the outcomes for each domain of the assessment are included in Table 13.

The results of this assessment show that the studies had a low risk of bias across most domains, with only a moderate risk of bias in the confounding domain. The primary endpoint of these studies (ability of imlifidase to decrease levels of anti-HLA antibodies within 24 hours to make the patient eligible for kidney transplantation) is not obviously susceptible to any known confounding within the population of the studies. Patients were only recruited to the studies if they were confirmed as highly sensitised patients with proven high levels of anti-HLA antibodies. For this group of patients, there are no documented potential confounding factors in the analysis. However, the potential for confounding cannot be ruled out with certainty, which leads to the assessment being given a moderate risk of bias. Overall, these studies

can be considered to be strong and robust (within their limitations as non-randomised studies).

Table 13 Summary of ROBINS-I risk of bias assessment of clinical trials

Domain	13-HMedIdeS-02	13-HMedIdeS-03	14-HMedIdeS-04	15-HMedIdeS-06
Confounding	Moderate	Moderate	Moderate	Moderate
Selection of participants	Low	Low	Low	Low
Classification of interventions	Low	Low	Low	Low
Deviations from intended interventions	Low	Low	Low	Low
Missing data	Low	Low	Low	Low
Measurement of outcomes	Low	Low	Low	Low
Selection of the reported result	Low	Low	Low	Low
Overall bias	Moderate	Moderate	Moderate	Moderate

These trials have been conducted in a more mixed patient population than has been included within the licence or that will receive this treatment in UK practice. In order to provide the most relevant data for this appraisal, the main data presented are within a subgroup of patients who match those that would be expected to receive this treatment in UK practice, as verified by UK-based clinical experts. Please see the meta-analysis section of this submission for further details (Section B.2.8). Therefore, the data presented from these trials can be seen to be generalisable to the UK patient population. Another aspect of the clinical trials is that they were conducted using standard treatment protocols for transplant at the study centres with minimal modifications required to incorporate imlifidase. Whilst this has led to a variation in the trial protocols, it demonstrates that imlifidase can fit into a variety of current treatment protocols. Therefore, the trials can be considered generalisable to the UK despite the trial protocols not using a UK specific transplant treatment protocol.

The main limitations of these data are that they only contain a relatively small number of patients and that the studies are of a non-randomised and non-controlled design. In order to best utilise the data available, a pooled analysis of all available

(relevant) data will be presented. This maximises the group size available for analysis, without further large clinical trials being conducted. Due to the scarcity of suitable candidates for clinical trials of imlifidase, a balance was necessary between the time required to collect sufficient data to show the efficacy of imlifidase and the overall number of subjects included in these trials. The clinical trials conducted reflect the orphan indication being treated and can therefore be seen to be appropriately sized for the limited patient population available. This has consequently led to a relatively small number of patients within these trials, but nevertheless an adequate population has been included to provide sufficient data to demonstrate the efficacy of imlifidase. The nature of imlifidase treatment and kidney transplant impose ethical barriers on conducting controlled trials. It would be unethical to conduct a randomised controlled trial in this case due to the lack of a safe and effective alternative therapy option to act as a comparator (available desensitisation protocols are currently experimental off-label treatments which are not suitable for use with a deceased donor transplant). Therefore, it was not possible to conduct randomised, controlled trials of this treatment. Additionally the scarcity of donor organs and the differences in kidney allocation systems between countries are further barriers to conducting a randomised controlled trial. However, it is not felt that these factors should unduly affect the generalisability of these data to UK practice.

B.2.6 Clinical effectiveness results of the relevant trials

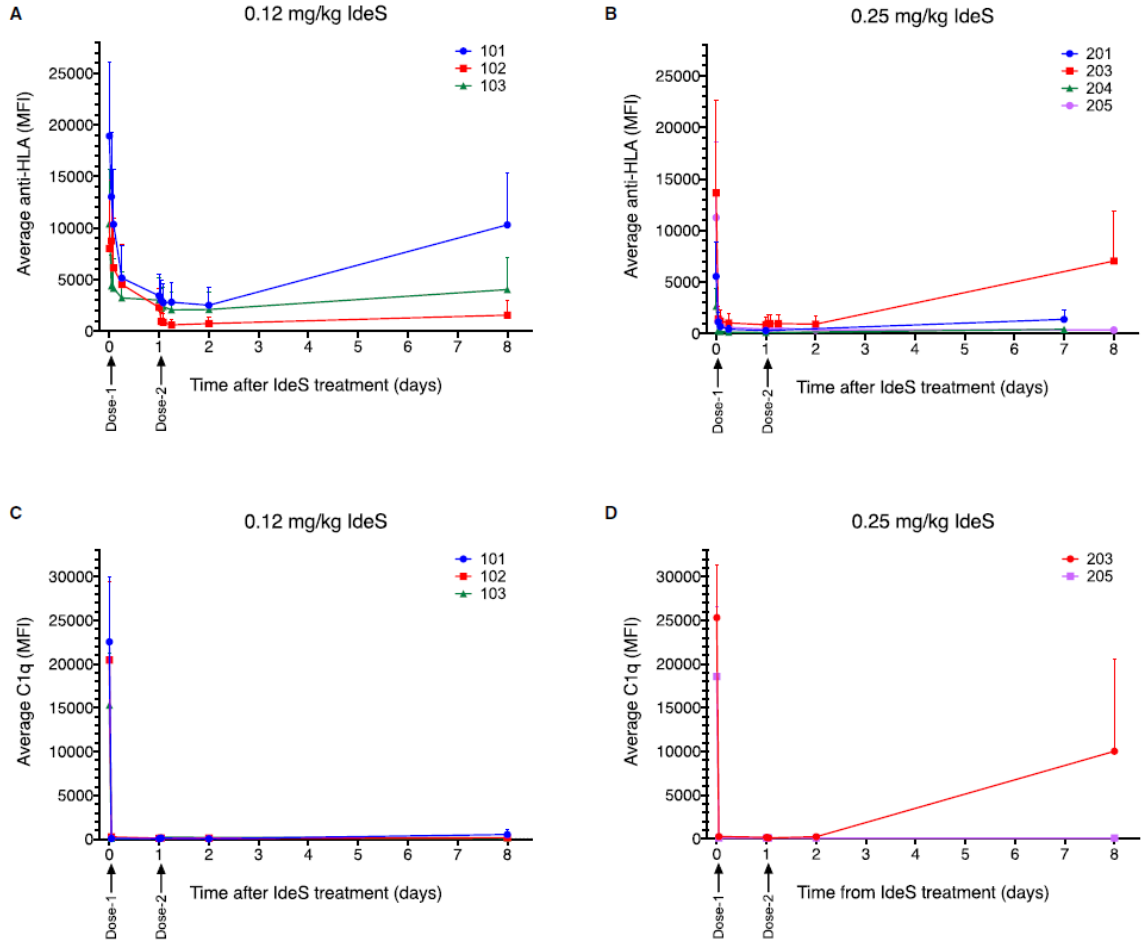
B.2.6.1 13-HMedIdeS-02

All efficacy outcomes were based on the FAS. Seven patients received the planned dose; three patients received 2 doses of 0.12mg/kg, i.e. 0.24mg/kg in total (Group 1), two patients received 0.25mg/kg (Group 2), and two patients received two doses of 0.25mg/kg, i.e. 0.50mg/kg in total (Group 2). One patient was to receive 0.25mg/kg once but the infusion was stopped after approximately 4 minutes due to suspected infusion reactions.

B.2.6.1.1 Reduction in anti-HLA antibody levels allowing for transplantation (primary endpoint)

In all patients, imlifidase led to a reduction in MFI in SAB assays, which reflects the reduced binding of anti-HLA antibodies and complete elimination of C1q binding within a few hours after the first dose.[63] After completion of treatment, the mean MFI of anti-HLA antibodies with a pre-dose MFI of >1100 in the three patients in Group 1 (two x 0.12mg/kg dose of imlifidase) was reduced from 18,900, 8000, and 10,400 to 2500, 610, and 2100, respectively.[63] The mean MFI in the four patients in Group 2 (one/two x 0.25mg/kg dose of imlifidase) was reduced from 5600, 13,700, 2700, and 11,300 to 290, 850, 110, and 350, respectively.[63] These results are illustrated graphically in Figure 3. A stronger and more rapid effect was seen in patients treated with 0.25mg/kg compared with patients treated with 0.12mg/kg. Additionally, within Group 1 patients the second dose produced a clear additional reduction, but a similar effect was not observed within those Group 2 patients receiving two doses of 0.25mg/kg. This effect is likely to be because the Group 2 patients had already exhibited a more complete reduction of MFI after the first (greater) dose.

Figure 3 Measured antibody levels with imlifidase treatment (for antigens with pre-dose MFI >1100)[63]



Numbers on graph legends (101,102 etc.) refer to individual patient identifiers. A & B show average (+ standard deviation) of anti-HLA antibodies before and after imlifidase treatment in patients treated with 2 doses of 0.12mg/kg imlifidase (A) or 1/2 doses of 0.25mg/kg imlifidase (B). C & D show average (+ standard deviation) C1q-binding antibodies before and after imlifidase treatment in patients treated with 2 doses of 0.12mg/kg imlifidase (A) or 1/2 doses of 0.25mg/kg imlifidase (B). HLA: human leukocyte antigen; IdeS: imlifidase; MFI: mean fluorescence intensity

Further data show that anti-HLA MFI values began to recover from Day 7 or 8 after completion of imlifidase treatment.[63] These values returned to pre-dose levels between Day 14/15 and Day 28 for all patients except for one, who received an HLA-incompatible kidney transplant during the study and thus received immunosuppressive treatment as standard of care post-transplant.[63] The results show that no patient in Group 1, but 3 out of 4 patients in Group 2 reached the primary endpoint of this study (i.e. anti-HLA antibody levels that are considered acceptable for transplantation defined as a 90th percentile MFI value <1100).[63] This

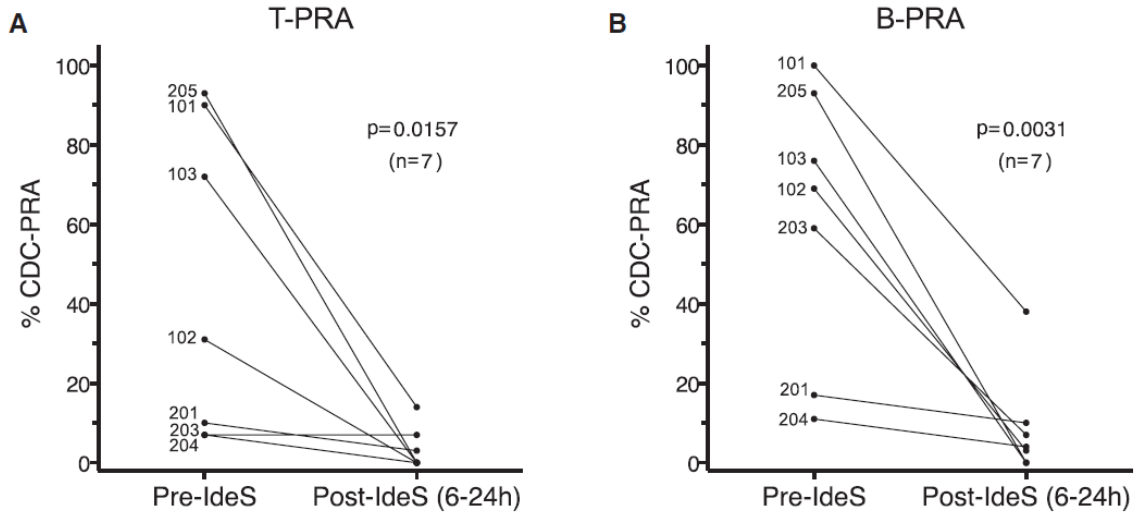
shows that a single dose of imlifidase at 0.25mg/kg (with the occasional need for a second dose) was sufficient for the majority of patients to reach the primary endpoint criteria. Based on these results, there is a clear demonstration of the efficacy of imlifidase in reducing DSA levels to those that would allow for a transplant to proceed.

The SAB-C1q results show that both 0.12 and 0.25mg/kg imlifidase almost completely eliminated the MFI signal, with a considerable reduction in C1q binding one hour after a single dose (Figure 3).[63] There was no clear additional effect of a second dose. SAB-C1q MFI levels began to increase again on Day 8 but did not return to the pre-dose levels during the 9-week study period.[63]

B.2.6.1.2 Reduction of PRA levels and FACS crossmatch results

All patients displayed a significant reduction in pre-dose PRAs within 1 hour of imlifidase treatment.[63] Within 24 hours after first imlifidase treatment, there was a large reduction in T-cell and B-cell PRAs (p=0.0157 and 0.0031, respectively) with very low post-treatment PRAs (Figure 4).[63] There was large individual variation in the rate of PRA recovery, but most patients started to show a recover between Days 7 and 14.[63] The results show that after imlifidase treatment, 86% (6/7 patients) became crossmatch negative with antibody incompatible hypothetical donors.[63]

Figure 4 Panel reactive antibody levels with imlifidase treatment



A shows T-cell non-amplified CDC-PRA. B shows B-cell non-amplified CDC-PRA. CDC: complement dependent cytotoxicity; IdeS: imlifidase; PRA: panel reactive antibodies

B.2.6.1.3 Other

The pharmacokinetic results from this study showed that maximum plasma concentration (C_{max}) was reached at the end of the 15-minute infusion or shortly thereafter.[63] In those patients that received a second dose, the second C_{max} was higher than the first.[63] The fast distribution phase had a mean half-life of 5 hours and the slow elimination phase had a mean half-life of 70 hours (range 50–300 hours).[63] These results indicate that the distribution and elimination parameters of imlifidase for patients with CKD were similar to those observed in healthy subjects.[63]

The efficacy of imlifidase on IgG degradation was investigated, and it was found that in Group 1 mean IgG concentration was reduced from 11g/L (baseline) to 2.2g/L after 6 hours and to 0.61g/L after 24 hours from dose 1.[63] After the second dose of imlifidase for Group 1, there was a further reduction in mean IgG to 0.021g/L.[63] For Group 2 patients, mean IgG concentration in those who received one dose reduced from 9.2g/L (baseline) to 0.096g/L after 6 hours and to 0.030g/L after 24 hours.[63] For Group 2 patients, mean IgG concentration in those who received two doses reduced from 9.5g/L (baseline) to 0.17g/L after 6 hours and to 0.017g/L after 24 hours from dose 1.[63] After the second dose, the mean IgG concentration was reduced to <0.01g/L.[63] The results of the SDS-PAGE analysis confirmed the ELISA results.[63]

The assessment of anti-drug antibodies found that, as observed previously, all patients had detectable anti-imlifidase IgG levels at baseline, with a median of 11mg/L (range 8.6–19mg/L).[63] After dosing, the levels of these antibodies dropped below the lower limit of quantification due to the cleavage of antibodies by imlifidase.[63] Anti-imlifidase IgG concentrations increased from Day 7 after treatment in all patients to a peak at Day 14 (except for in the transplanted patient who exhibited highest concentrations at Day 64).[63] There was a substantial individual variation in the magnitude of anti-imlifidase response, with a median peak concentration of 875mg/L and a range between 190 and 1000mg/L.[63] On Day 64, the median serum concentration had dropped to 120mg/L (range 87–280mg/L).[63]

These results demonstrate that imlifidase leads to a rapid degradation of IgG antibodies, as expected through its mechanism of action. The development of an immune response against imlifidase is not unexpected, but as imlifidase treatment

leads to the immediate degradation of these antibodies, they have little impact of the efficacy of this treatment. As imlifidase is designed for a single administration (or a second dose immediately following the first), the long-term impact of these anti-drug antibodies is not relevant to the efficacy of this product. However, it is worth noting that the level of these antibodies do reduce over time.

B.2.6.1.4 Conclusions

The primary objective of this study was to find an imlifidase dosing regimen in which the majority of patients results in anti-HLA antibody levels acceptable for transplantation within 24 hours from dosing. This objective was fulfilled since all subjects reached the modified primary endpoint. Imlifidase was able to successfully lower anti-HLA levels in patients to a sufficient level to allow kidney transplantation to occur.

B.2.6.2 13-HMedIdeS-03

In this study, five patients received a single dose of 0.25mg/kg and five patients received a single dose of 0.50mg/kg imlifidase.

B.2.6.2.1 Safety parameters (primary endpoint)

The primary endpoint of this study was defined as being the safety parameters. These results are not reported here, and are included within the data presented as part of the adverse reactions section of this report. The study concluded that no safety concerns were raised by this study beyond those expected from previous studies.

B.2.6.2.2 Reduction in anti-HLA antibody levels allowing for transplantation

After imlifidase treatment, all 10 patients were able to undergo kidney transplantation, with both imlifidase doses (0.25mg/kg and 0.50mg/kg) being able to result in anti-HLA antibody levels acceptable for transplantation and negative crossmatch tests.

At baseline, all 10 patients had anti-HLA antibodies in the SAB assay with MFI >3000. The reduction in MFI value from baseline following imlifidase treatment was

rapid and similar between dose groups. In both dose groups, the median MFI values decreased quickly and reached their minimum between 6 and 24 hours post-imlifidase. The 0.25mg/kg dose of imlifidase resulted in minimum median MFI values in the range [redacted] at 24 hours, and the 0.50mg/kg dose led to minimum median MFI values in the range [redacted] at 6 hours [redacted] and at 24 hours [redacted]. Anti-HLA antibodies started to increase on Day 7 and in most patients, levels returned to baseline between Day 14 and 30. In all patients, the median MFI values of positive SAB-C1q antibodies declined rapidly after imlifidase dosing and were stable from [redacted] at a median MFI level of [redacted]. Eight of the 10 patients had DSAs at baseline, ranging from 1 to 5 per patient, with similar rates in both dose groups. The median MFI value of DSAs reduced rapidly after dosing and reached the lowest median MFI levels [redacted] post-imlifidase, at approximately [redacted] in the low dose group [redacted] in the high dose group. The DSA levels remained low until Day 7 in most patients.

B.2.6.2.3 FACS and CDC crossmatch results

All patients underwent B- and T-cell crossmatch analyses. Prior to imlifidase treatment, in the FACS crossmatch test, six patients were crossmatch positive (two were both T- and B-cell positive, two were T-cell positive only, and two were B-cell positive only). In the CDC crossmatch test, one patient was B-cell positive. All positive crossmatches were converted to negative 2–24 hours post-imlifidase treatment (Table 14).

Table 14 Crossmatch test results before and after imlifidase

	FACS crossmatch (n = 10)					**CDC crossmatch (n = 10)**			
	Pre-dose		**Post-dose**			**Pre-dose**		**Post-dose**	
	T +	**T -**	**T +**	**T -**		**T +**	**T -**	**T +**	**T -**
B +	2	2	-	-	**B +**	-	1	-	-
B -	2	4	-	8*	**B -**	-	9	-	7*

*Post-dose FACS crossmatch (2 patients) and CDC crossmatch (3 patients) not determined (these patients were crossmatch negative in these tests pre-dose). CDC: complement dependent cytotoxicity; FACS: fluorescence-activated cell sorting

B.2.6.2.4 Reduction of PRA levels

Both B- and T-cell PRA levels decreased rapidly after imlifidase. The greatest decrease occurred between pre-dose (B-cell = [redacted], T-cell = [redacted]) and 1

hour post-dose (B-cell [redacted], T-cell [redacted]) (Figure 5). The mean B- and T-cell PRA levels [redacted].

Figure 5 Mean panel reactive antibody levels before and after imlifidase

[redacted]

[redacted]

B.2.6.2.5 Time to recovery of total serum IgG and anti-HLA antibody

Time to recovery of total serum IgG occurred earlier in the high dose group than the low dose group. In the low dose group, [redacted] patients had a time to recovery of [redacted] with [redacted]. In the high dose group, [redacted] had a time to recovery of [redacted], while [redacted].

Time to 80% recovery of anti-HLA antibodies in the SAB assay also occurred earlier in the high dose group than in the low dose group. The median time to recovery was [redacted] in the low dose group, and [redacted] in the high dose group. [redacted].

B.2.6.2.6 Kidney function

At the end of the study (180 days post-transplantation), all kidneys were functioning with serum creatinine values within the expected range for successfully transplanted patients (<200µmol/L). The eGFR was >60mL/min/1.73m^2 in one patient in each dose group [redacted], between 30 and 59mL/min/1.73m^2 in three patients in each dose group [redacted], and <30mL/min/1.73m^2 in one patient in each dose group [redacted]. Kidney biopsy was normal for all patients in the 0.25mg/kg dose group and for two patients in the 0.50mg/kg dose group. Of the remaining three patients in the high dose group, [redacted] and [redacted] displayed chronic donor-related changes (interstitial fibrosis and tubular atrophy). Importantly, however, the donor kidneys were functional in all cases.

B.2.6.2.7 Conclusions

Both of the imlifidase doses investigated within this study were successfully able to remove anti-HLA antibodies, such that crossmatch conversion was achieved. This demonstrates that a dosing of 0.25mg/kg of imlifidase is sufficient to achieve this important goal in sensitised patients prior to transplant. These changes were sufficient to allow transplantation to occur. The donated kidneys gained the expected level of function for a transplanted organ in all cases (compared to figures within the UKRR Annual Report).[9] This study therefore demonstrates that desensitisation with imlifidase can be achieved within a few hours and can lead to a successful transplant outcome.

B.2.6.3 14-HMedIdeS-04

In this study, all 17 study patients received 0.24mg/kg imlifidase.

B.2.6.3.1 Number and levels of DSAs pre- and post-transplantation (primary endpoint)

Before imlifidase, all patients had between one and 12 identified DSAs, and 15 of the 17 patients had between one and 5 DSAs that had MFI value >2000. After imlifidase treatment, MFI values decreased rapidly and, for all except one patient, DSAs showed MFI values <2000 at both 6 and 24 hours post-imlifidase treatment [redacted]

[redacted]. At 30 days post-treatment/transplantation, the DSA MFI levels in all patients had increased, but were below the pre-dose values [redacted]. At the end of study (6 months post-imlifidase and transplantation, or after 3 months for some subjects without a 6-month record), [redacted] did not have any DSAs with MFI >2000 [redacted].

B.2.6.3.2 Incidence of allograft rejections (primary endpoint)

At the end of the study, 16 out of 17 patients (94%) had a functioning kidney. DGF function was experienced by [redacted] at various time periods. These required concomitant dialysis for [redacted], but there was no correlation to cold ischemia time or kidney donor profile index. However, all of these grafts were functioning at the end of study (Day 180). One patient (6%) suffered a hyperacute AMR and immediate graft loss on Day 1. This was considered as being IgM and/or IgA mediated. No intact IgG was detected at the time of the rejection indicating that imlifidase had been efficacious at this point.

B.2.6.3.3 Renal function by creatinine, eGFR, and urine protein measurements (primary endpoint)

Proteinuria (generally mild or moderate) was seen in 10 of 13 patients (77%) with data one week post-imlifidase and transplantation. Proteinuria subsequently decreased and at one month post-transplantation, 13 of 16 patients (81%) had no observed proteinuria, which remained unchanged to Day 180 (end of study).

The mean serum creatinine reduced throughout the study period from above 900µmmol/L pre-transplantation to below 200µmmol/L three weeks post-transplantation, albeit with a large degree of individual variation (range 44-592µmmol/L). Consequently, the corresponding eGFR increased from very low levels to a mean 49mL/min/1.73m^2 at three weeks with a similar degree of variation (range 10-157mg/mL/1.73m^2), and continued to improve throughout the study. At Day 180, 16 patients (94%) had functioning kidneys, nine (56%) of these had eGFR ≥60mL/min/1.73m^2, six (38%) had eGFR between 30 and 59mL/min/1.73m^2, and only one patient (6%) had eGFR below 30mL/min/1.73m^2 [redacted].

B.2.6.3.4 Biopsy pathology evaluation (primary endpoint) and antibody-mediated rejection

All but one patient had a functioning kidney at the end of the study. Nine rejection episodes were reported as adverse events by eight (47%) patients. One of these was a hyperacute non-IgG mediated AMR with subsequent immediate graft loss on Day 1. Two episodes of post-treatment emergent biopsy-confirmed AMR were identified in two (13%) patients. One mixed AMR and cell mediated rejection (CMR), judged as chronic, occurred 2 months after transplantation in one (6%) of the 16 patients with functioning kidneys, and one active AMR and CMR was identified from the protocol-specified biopsy, but was without clinical signs of ongoing deterioration of the kidney function, and therefore was defined as subclinical AMR.

B.2.6.3.5 Safety parameters (primary endpoint)

One of the primary endpoints of this study was the safety parameters. These results are not reported here, and are included within the data presented as part of the adverse reactions section of this report. The study concluded that no subjects were withdrawn due to an adverse event, and none of the treatment-emergent adverse events were regarded to be related to treatment with imlifidase.

B.2.6.3.6 Conclusions

Efficacy of imlifidase was shown with a rapid decrease in DSA levels that allowed for transplantation to occur successfully. Kidney function was delayed in [redacted] of transplants, which required up to [redacted] of dialysis. By the end of the study, 94% of kidney transplants were functional (the only exception was in the one patient who experienced hyperacute rejection [not IgG-mediated]). Imlifidase was therefore able to successfully allow transplant within these highly sensitised patients.

B.2.6.4 15-HMedIdeS-06

In this study, 15 patients received one dose of 0.25mg/kg, three patients received two doses of 0.25 mg/kg and one patient received a total dose of approximately 4 mg corresponding to 0.058 mg/kg. Therefore, of the 19 patients exposed, 18 patients received the planned dose(s), whilst one patient received less than 25% of the planned dose due to an infusion related reaction that resulted in withdrawal of study drug.

B.2.6.4.1 Ability to create a negative crossmatch test (primary endpoint)

Of the 19 patients who received imlifidase dosing, 17 (89%) were converted from a positive to a negative crossmatch on the FACS crossmatch test (Table 15). Of the two patients (11%) who did not have complete crossmatch conversion, one had a positive FACS T-cell crossmatch test with borderline reactivity 24 hours post-dose which could not be correlated to the presence of DSAs and thus this data was interpreted as not clinically significant. A virtual crossmatch test was negative at 2 hours post-dose, and based on an overall assessment, it was decided to transplant the patient. The second patient had the drug infusion discontinued and the patient was withdrawn from the study due to an adverse event. Therefore, all 18 patients who received one or two complete imlifidase dose(s) had crossmatch responses making them eligible for transplantation within the required 24 hour time period.

Table 15 Crossmatch test results before and after imlifidase

	FACS crossmatch (n = 18)			
	Pre-dose*		Post-dose	
	T +	T -	T +	T -
B +	5	12	0	0
B -	0	0	1[#]	17

*One patient was T+ but was not analysed for B-cell crossmatch (not enough cells);
[#]Borderline flow crossmatch but negative virtual crossmatch (judged as not clinically significant). FACS: fluorescence-activated cell sorting

B.2.6.4.2 DSA levels at pre- and post-imlifidase treatment

All patients had between one and 12 identified DSAs at baseline. Of the 18 patients with HLA data who received a transplant, 17 had at least one DSA with MFI value >3000 at pre-dose. Median DSA levels declined rapidly after imlifidase, [redacted]. Two hours post-dose, 11 patients had MFI values for all DSAs <3000. The remaining seven patients had MFI values for all DSAs <3000 at varying post-dose time points: 6 hours (four patients), 48 hours (one patient), 96 hours (one patient), and on Day 90 (one patient).

Median DSA levels started to increase again between [redacted] post-dose. At the end of the study (Day 180, or Day 120 and Day 64 [for two patients with no data at Day 180]), all DSA values were <3000 for [redacted] had one or more

DSAs which were >3000 MFI but remained below the pre-dose level, while [redacted] had a DSA that was above the pre-dose level from Day 21 until the end of the study.

B.2.6.4.3 Kidney function

Of the 18 transplanted patients, [redacted] had a functioning kidney at 6 months after transplantation (end of study). At baseline, serum creatinine was above normal range for most patients. However, at 6 months post-transplant, four patients had creatinine values within the normal range and an additional nine patients had creatinine levels in the range normally found in successfully transplanted patients (<200µmol/L). After 6 months, four (25%) patients had eGFR values >60mL/min/1.73m^2, 11 (69%) patients had an eGFR between 30 and 59 mL/min/1.73m^2, and only one (6%) patient had an eGFR <30 mL/min/1.73m^2 (value of 20.5mL/min/1.73m^2). At 6 months, proteinuria was negative for four patients and positive for nine patients.

DGF was reported by [redacted] with onset at 2–4 days after transplantation. All patients required dialysis, except [redacted] for whom DGF resolved within one day. For [redacted] of the patients with DGF, [redacted]. Two patients lost their grafts, [redacted]. Both grafts were non-functioning from the transplantation, [redacted]. Nine episodes in nine patients were biopsy-confirmed AMRs, of which six episodes were regarded as active AMRs and three as subclinical AMRs. All resolved during the study with standard immunosuppressive treatment. At end of study, 6 months after administration of imlifidase and transplantation, evaluation of graft biopsies [redacted].

B.2.6.4.4 Conclusions

Imlifidase was shown to be able to lead to a crossmatch conversion at 24 hours in 89% of patients, and 89% of patients also had no DSA with MFI >3000 at 48 hours post-treatment. This allowed a transplantation to occur, with 89% being functional at 6 months post-transplant. The two non-functioning grafts were lost, but neither was due to AMR. DGF occurred in [redacted], which mostly required dialysis before it resolved. Overall, imlifidase was able to successfully allow transplant within these patients.

B.2.7 Subgroup analysis

No pre-defined subgroup analyses were specified within the studies of imlifidase (see Appendix E). The NICE scope outlines the following subgroups of potential interest for this appraisal: recipients of kidneys from living donors; recipients of kidneys from deceased donors; low risk ('delisted') recipients of donor kidneys, non-delisted recipients of donor kidneys; degree of sensitisation in terms of antibody levels.

Due to the indication for imlifidase, a number of these subgroups are not relevant to this submission. The indication for imlifidase restricts its use to deceased donors only. This means that a consideration of recipients of kidneys from living donors is not appropriate for this appraisal as it would fall outside the marketing authorisation. Another subgroup identified was low risk ('delisted') recipients of donor kidneys. In this sense, delisting refers to the practice of removing low risk unacceptable antigens from consideration in order to allow for a negative crossmatch to be made. As these transplants are considered as a negative crossmatch, this again falls outside the marketing authorisation for imlifidase, which requires a positive crossmatch. Hansa Biopharma AB also does not consider the subgroup of degree of sensitisation to be particularly clinically appropriate for this appraisal. There are no internationally agreed definitions of a highly sensitised patient (the patient population that imlifidase is indicated for), and a variety of measures used in different countries (cRF, cPRA etc.). This makes consideration of subgroups stratified by degree of sensitisation challenging. In addition, any patients who are highly sensitised should be considered eligible for imlifidase, with a clinical judgement on the applicability of this treatment

being made based on the patient-specific immunological profile and the expected likelihood of transplant otherwise. Therefore, degree of sensitisation was not considered to be specifically relevant to this appraisal and has not been considered further.

The subgroups considered most relevant to this appraisal are recipients of kidneys from deceased donors, and non-delisted recipients of donor kidneys (as this matches the indication for this treatment). Due to the number of patients that have been treated with imlifidase during its clinical trials, and in order to maximise the data available, a combined analysis has been conducted (and is presented in the following section). This combined analysis focussed on a subgroup of the most relevant patients for this appraisal, and so only includes patients who received a deceased donor kidney and who were non-delisted (had a positive crossmatch). The target patient population for imlifidase is outlined in Section B.1.3.3, and covers highly sensitised patients within the KOS who may be either in Tier A or Tier B (at treating physicians discretion) who are unlikely to be transplanted. Full details on the patients included in this group and the associated results are included in the following section.

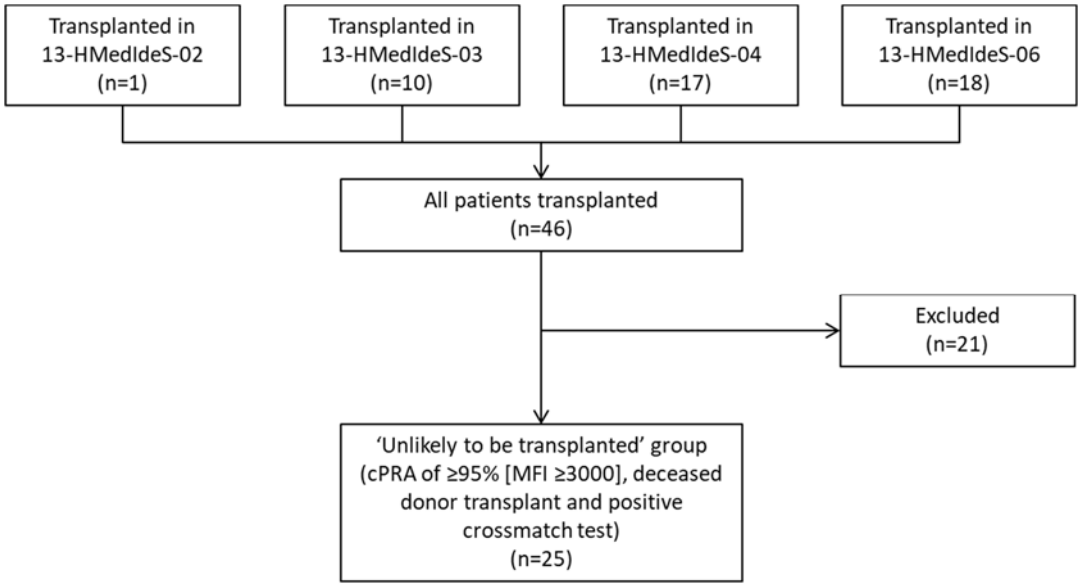
B.2.8 Meta-analysis

The analyses presented in this section are combined analyses of patients across a number of the clinical trials of imlifidase. The first of these is the results of an analysis published by Jordan et al. (2017),[5] which forms the main publication (to date) of results from imlifidase clinical trials. This study included the results from 25 patients who received a transplant during the trials: 13-HMedIdeS-02, 13-HMedIdeS-03, and 14 HMedIdeS-04.[5]

A separate analysis of the most relevant patients for this appraisal from all of the imlifidase trials described above (i.e. 13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06) is then also included. Within these studies, a total of 46 patients with varying levels of anti-HLA antibodies and DSA were transplanted following imlifidase treatment. The median age of these patients was 43 years (range 20-73), 46% were female, 76% were Caucasian and [redacted]% of the patients had blood group O (these patients tend to accumulate on the transplant

waiting list since they are only offered allografts from blood group O donors). The majority of patients (69%) had undergone at least one previous transplantation, with multiple transplantations recorded for several patients; patients had a median time on dialysis of 4.9 years. However this mixed population included some living donor recipients (n=7) who fall outside of the indication for imlifidase. There were also a small number of patients who did not show a positive crossmatch to the allocated kidney, which again falls outside of the indication for imlifidase. Therefore, an analysis of the most relevant population to UK clinical practice was considered to be a group designated 'unlikely to be transplanted' (which again matches the group suggested by the indication). This was defined based on expected European criteria for such a group as a cPRA of ≥95% (MFI ≥3000), deceased donor kidney offer and positive crossmatch test (in the early studies [13-HMedIdeS-02 and 13-HMedIdeS-03] there was less focus on recruiting highly sensitised patients than in later studies. Hansa Biopharma AB believes that this population matches with the proposed UK usage of this product, as confirmed by clinical expert opinion. Hansa Biopharma AB also believes that as there is not an accepted definition for this patient group that the decision to treat with imlifidase should be left to the treating physician's discretion. The criteria chosen for this analysis were not tied to any particular guideline or specific clinical practice, and were used purely to define a population for this analysis which matches the expected European patient population. Within the available patients, 25 met these criteria and formed the group for the analysis presented below.

Figure 6 Derivation of 'unlikely to be transplanted' group



cPRA: calculated panel reactive antibodies; MFI: mean florescence intensity

B.2.8.1 Jordan et al. (2017)[5]

The demographics for this combined patient group of 25 patients (one patient from 13-HMedIdeS-02, 10 from 13-HMedIdeS-03 and 14 from 14-HMedIdeS-04) are provided in Table 16. Patients had an average age of 46 and there was a relatively even split between men and women (with a slightly higher proportion of women). Almost all patients received a kidney from a deceased donor and most had received at least one previous kidney transplant.

Table 16 Demographics of patients in Jordan et al.

		Total (n=25)
Age (years)	**Mean (SD)**	46.2 (14)
Sex, n (%)	**Female**	14 (56.0%)
	Male	11 (44.0%)
Deceased donor status	**n (%)**	23 (92.0%)
Cold ischaemia time, hours	**Mean (SD)**	15.8 (7.5)
Number of previous renal transplants	**≥1, n (%)**	14 (56.0%)

SD: standard deviation

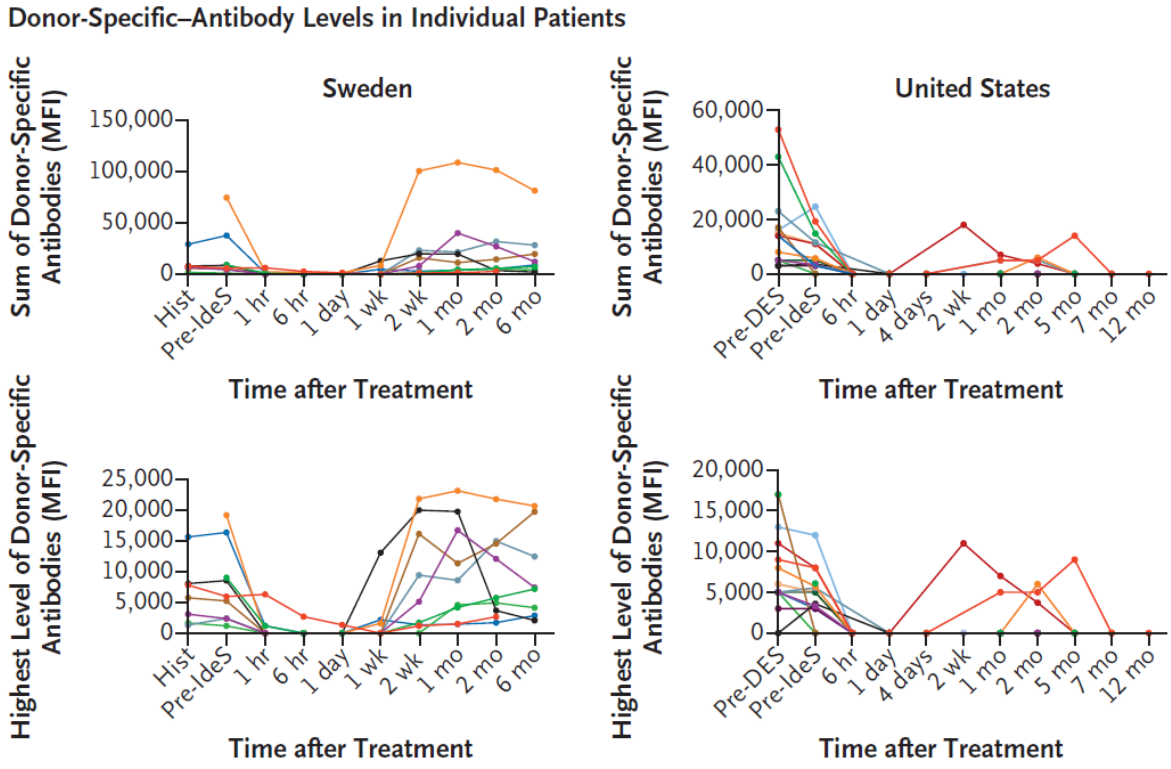
B.2.8.1.1 DSA antibody elimination

The levels of anti-HLA antibodies and DSA were substantially and significantly reduced in all patients, at between 6 and 24 hours after treatment. Levels of anti-HLA antibodies and DSA remained undetectable until 7 to 14 days after

transplantation, after which time a rebound in these antibody levels occurred. In addition, a near-complete inhibition of C1q-binding anti-HLA antibodies was seen 1 hour after treatment.

Data on DSA levels are presented in Figure 7, which shows these data separately for the two countries from which data were derived. These illustrate the impact on DSA described above. It is worthy of note that despite similar DSA levels before transplantation, there were significant reductions in the DSA seen post-transplantation in the US patients. This was explained as being likely due to the use of IVIg and rituximab in the US patients before and after transplant.

Figure 7 Donor specific antibody levels as reported in Jordan et al. (reproduced from Jordan et al.[5])



DES: desensitisation; Hist: historical; IdeS: imlifidase; MFI: mean fluorescence intensity

B.2.8.1.2 Transplant-related outcomes

Delayed graft function was experienced by 42% (10/24) of patients, which required dialysis until it resolved (median of 6 days). DGF was reported significantly more frequently within the US patients of this study (p<0.001); however, cold ischaemia time was also significantly longer in the US patients (19.9 hours vs 10.6 hours,

p<0.001) which may have contributed to the rates of DGF seen. Renal function was generally good in the transplanted patients, with reduced serum creatinine levels and a mean eGFR at 1-6 months post-transplant of 58mL/min/1.73m^2. Kidney function was therefore seen to be in line with expectations for highly sensitised, post-transplant patients.[74,75,76]

Within the transplanted patients there was one instance of hyperacute rejection that occurred (despite a negative crossmatch and DSA assessment pre-transplant). Further investigation into this case established high-titre IgM and IgA antibodies that were reactive to donor-allograft endothelium; however, there was no evidence of IgM anti-HLA or DSA, and thus this rejection event was concluded to have been caused by a non-HLA antibody that cannot be cleaved by imlifidase. Given the known rebound in IgG levels after approximately two weeks following imlifidase treatment, it is not expected that imlifidase treatment will impact rejection events at other time points. There were three Swedish patients who experienced AMR at a mean of two weeks post-transplant. Biopsies performed at six months (per protocol) revealed minimal inflammation in 9 of the 11 Swedish patients. For the US patients, seven patients had inflammation on biopsy (at a mean of 3.6 months), with two of these cases reaching the criteria for consideration as AMR. Both of these cases resolved after accepted immunosuppressive treatment.

B.2.8.1.3 Conclusions

The Jordan et al. publication concluded that imlifidase was able to demonstrate a significant reduction in IgG anti-HLA levels that led to DSA levels that were considered acceptable for transplant.[5] Transplants were successful in 24 of 25 cases (with the one hyperacute rejection due to a non-HLA antibody), and outcomes were good in all of these cases.[5] Imlifidase treatment can therefore be seen as an effective intervention for reducing or eliminating DSA before transplantation.[5]

B.2.8.2 Combined analysis of most relevant patients

B.2.8.2.1 Demographics

The demographics for the combined patient subgroup (defined as cPRA of ≥95% [MFI ≥3000], deceased donor transplant and positive crossmatch) are provided in

Table 17. The demographics of this combined subgroup are similar to the overall demographics of all transplanted patients.

Table 17 Demographics of combined analysis subgroup

		Total (n=25)
Age (years)	**Mean (SD)**	[redacted]
	Range	[redacted]
Sex, n (%)	**Female**	[redacted]
	Male	[redacted]
Race, n (%)	**White**	[redacted]
	Black	[redacted]
	Other	[redacted]
Weight (kg)	**Mean (SD)**	[redacted]
	Range	[redacted]
Body mass index	**Mean (SD)**	[redacted]
	Range	[redacted]
Mean time on dialysis before transplant (years)	**Mean (SD)**	[redacted]
Hepatic impairment at inclusion	**n (%)**	[redacted]
Cardiovascular disease at inclusion	**n (%)**	[redacted]
Diabetes at inclusion	**n (%)**	[redacted]
Autoimmune disorder at inclusion	**n (%)**	[redacted]
Number of previous renal transplants	**0, n (%)**	[redacted]
	1, n (%)	[redacted]
	2, n (%)	[redacted]
	3, n (%)	[redacted]
Deceased donor status	**n (%)**	[redacted]
Organ storage	**Simple cold storage, n (%)**	[redacted]
	Hypothermic machine perfusion, n (%)	[redacted]
Cold ischaemia time, hours	**Mean (SD)**	[redacted]
	Range	[redacted]

SD: standard deviation

The baseline antibody status of the patients included within this subgroup are summarised in Table 18. These patients had a high level of sensitisation as evidenced by a mean of [redacted] DSAs, a mean MFI of >11,000 for the immunodominant antigen, and a median cPRA of 99.9%. Due to this high level of

sensitisation, these patients represent a population where it would be difficult to find a suitable transplant in current practice.

Table 18 Antibody status at baseline

		Total (n=25)
Number of DSA at baseline	**Mean (SD)**	[redacted]
Pre-treatment MFI of immunodominant antigen	**Mean (SD)**	[redacted]
	Median	[redacted]
cPRA	**Mean (SD)**	[redacted]
	Median	99.9
	Range	[redacted]
Pre-treatment FACS crossmatch, N(%)	**B-cell positive/ T-cell negative**	[redacted]
	B-cell negative/ T-cell positive	[redacted]
	B-cell positive/ T-cell positive	[redacted]

[redacted]. cPRA: calculated panel reactive antibodies; DSA: donor specific antibodies; FACS: fluorescence-activated cell sorting; MFI: mean fluorescence intensity; SD: standard deviation

B.2.8.2.2 Crossmatch conversion and DSA elimination (primary endpoint)

Crossmatch conversion was considered the key outcome in the clinical trials of imlifidase, as this conversion from a positive crossmatch to a negative crossmatch is a key indicator for risk of hyperacute graft rejection. The highly sensitised patients studied within this subgroup were classed as unlikely to receive a transplant and had proven DSAs that meant finding a negative crossmatch organ offer was challenging. The ability of imlifidase to allow for a conversion from crossmatch positive to crossmatch negative therefore allows for kidney transplantation to occur with a greatly reduced risk of hyperacute rejection mediated by these DSAs. This is also why this outcome formed one of the primary endpoints within all the clinical trials of imlifidase. In the patient group considered here, all patients had a positive FACS crossmatch before imlifidase treatment (see Table 19 for details on baseline crossmatch results). All of these were successfully converted to a negative crossmatch (one patient had borderline flow crossmatch and negative virtual crossmatch, this was judged as not clinically significant and transplant was carried out). This conversion occurred rapidly, generally within a few hours, making these

patients eligible for transplantation within the required time frame for a deceased donor transplant. All patients subsequently received a transplant.

Table 19 Crossmatch test results for imlifidase treatment in combined analysis subgroup

	Any positive crossmatch test pre-dose (n=25)	Any positive crossmatch test post-dose (n=25)
Number (%)	25 (100.0%)	1 (4.0%)*

*Borderline flow crossmatch and negative virtual crossmatch, this was judged as not clinically significant and transplant was carried out

Crossmatch conversion was confirmed by analysis of DSA using the SAB assay. This analysis focussed on those antibodies which had an MFI value of >3000 at baseline. This showed that two hours after imlifidase administration, [redacted] patients ([redacted]%) were devoid of any DSA that had MFI >3000, which rose to [redacted] patients ([redacted]%) after 24 hours. The MFI signals seen for the remaining patients were confirmed to be due to the presence of single chain IgG. These single chain IgG have a highly attenuated activity when compared with IgG, but are detected equally well by the SAB-HLA assay. Thus, this can be interpreted as a false positive signal, which can be seen to be confirmed by the crossmatch tests [redacted]. For the immunodominant antigens of each patient, the mean MFI dropped from [redacted] (median [redacted]) at baseline to [redacted] (median [redacted]) post-treatment. DSA levels remained undetectable for up to 7 days post-transplant before any rebound occurred, which allowed transplant to proceed. The mean MFI for the immunodominant antigens rose to [redacted] (median [redacted]) at Day 7, [redacted] (median [redacted]) at Day 14, and [redacted] (median [redacted]) at Day 30. This shows a slow and steady rebound in the DSA values, but which in most cases remained below the baseline levels seen.

B.2.8.2.3 Kidney function

The eGFR was used as a primary measure of kidney function. This showed that kidney function was good or satisfactory in all patients with a functioning kidney and available data. At six months, 40.0% of patients (8/20) had an eGFR of at least 60mL/min/1.73 m^2, 50.0% (10/20) had an eGFR of 30–59mL/min/1.73 m^2, and 10.0% (2/20) of the patients had an eGFR of <30mL/min/1.73 m^2. Limited long-term follow-up has shown that similar kidney function results were maintained for up to

two years post-transplant. Figures within the UKRR Annual Report show that the UK average was for just over 15% of prevalent transplant patients to have an eGFR of <30mL/min/1.73 m^2.[9] The kidney function outcomes for imlifidase compare favourably to these data and, therefore, can be considered in line with what would be expected following transplant. A formal long-term study is ongoing (see Section B.2.11 for details), that will be able to provide more details on the long-term outcomes in imlifidase patients in due course.

B.2.8.2.4 Patient and graft survival

At the end of the clinical trial periods (6 months), all patients were alive and 24 out of the 25 (96.0%) had a functioning graft (Table 20). The long-term follow-up data currently available (see Section B.2.11 for details on ongoing long-term study) showed a death-censored graft survival of [redacted]% at two years and overall patient survival of [redacted]% at two years. These rates of graft and patient survival are broadly in line with the figures for UK deceased donor transplants as reported in the National Health Service Blood and Transplant (NHSBT) Annual Report.[15] The NHSBT figures are for a first kidney-only graft whereas many of the imlifidase patients had received a previous kidney transplant. In addition, the small population size available for this analysis make comparison of figures challenging, but it is encouraging that these figures for graft survival can be seen to be in line with UK figures. Patient survival is slightly lower than the figures reported within the NHSBT Annual Report.[15] However, due to the small patient numbers available, this survival rate is diminished as a result of three recorded deaths, none of which were considered to be related to imlifidase or kidney malfunction. No other deaths were recorded within the wider imlifidase treated group, meaning that patient survival in the group of all patients undergoing transplant following imlifidase treatment was 91% at two years. This highlights that patient survival following transplant with imlifidase can be considered broadly in line with levels that would be expected, even though many of the imlifidase patients had received a previous kidney transplant.

Table 20 Survival in combined analysis group

	0–6 months	6 months–1 year	1–2 years
	n = 25	**n = 20**	**n = 16**
Graft survival, n (%)	24 (96.0%)	20 (100.0%)	16 (100.0%)
Patient survival, n (%)	25 (100.0%)	17 (85.0%)	16 (100.0%)

B.2.8.2.5 AMR

An acute rejection episode is the consequence of an immune response of the host attacking the transplanted organ or cells. Imlifidase acts to lower DSA levels over the initial period of a transplant to avoid hyperacute rejection. As imlifidase is not expected to impact other rejection events, this was not considered to be a primary efficacy outcome and so was also considered as a safety consideration. Therefore, data on rejection events in the safety population are presented within the safety data (see Section B.2.10.5). Briefly, 40.0% (10 of 25) of patients had diagnosed AMR confirmed by biopsy; of these, [redacted] patients had signs of AMR at the 6-month biopsy without any clinical signs, and thus were categorised as subclinical AMR. All patients with AMR were successfully treated according to local practice with standard immunosuppressive therapies. This shows that AMR occurred at rates in line with expectations (and literature reported values), and all instances were successfully treated using standard therapies with patients maintaining functioning grafts.

B.2.8.2.6 Conclusions

The results of this combined subgroup analysis demonstrate the efficacy of imlifidase in a patient population relevant to this appraisal. That is a patient group who were highly sensitised with high levels of DSA, who received a deceased donor kidney transplant despite a positive crossmatch before imlifidase treatment, making these patients unlikely to receive a transplant through other means. Imlifidase was able to rapidly induce a crossmatch conversion and remove DSA to low levels that facilitated a successful transplantation. Following transplant, the kidney function, graft survival and patient survival were all broadly in line with expectations and UK data for patients receiving a first kidney transplant. This is despite the fact that the study population consisted of highly sensitised patients who had mostly had previous failed kidney transplants.

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparison was conducted for this appraisal as it was not applicable, and no comparative data were available to inform such a comparison.

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

Not applicable

B.2.10 Adverse reactions

B.2.10.1 Summary and introduction

Within the four clinical studies of imlifidase reported herein (13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06) a total of 54 patients with CKD have received at least one dose of imlifidase. This includes patients outside the scope of this appraisal (for example some patients received a transplant from a living donor), but this wider group of patients was chosen to be reported here as the AEs would be expected to be similar within the specific patient population of interest and this approach allows for the largest group of patients to be included. A summary of the disposition of these patients is included in Table 21. This shows that almost all patients who received imlifidase went on to successfully receive a kidney transplant (85.2%), with the exception of 7 patients in study 13-HMedIdeS-02 (where it is important to note, transplant was not a pre-specified part of the trial protocol and only occurred at the investigators discretion if the possibility became available for a patient) and one patient in study 15-HMedIdeS-06 who experienced a SAE (and was the only patient to discontinue from the studies due to an AE). There were also only four patients (7.4%) who had drug withdrawn or their dosing interrupted, and in two of these cases dosing was able to resume and a full dose was successfully administered.

Table 21 Summary of patients in safety data set

	13-HMedIdeS-02	13-HMedIdeS-03	14 HMedIdeS-04	15-HMedIdeS-06	Total
Received at least one dose of imlifidase	8	10	17	19	54
Received transplant	1 (12.5%)	10 (100.0%)	17 (100.0%)	18 (94.7%)	46 (85.2%)
Did not receive transplant	7* (87.5%)	0	0	1† (5.3%)	8 (14.8%)
Completed core study	8 (100.0%)	10 (100.0%)	15 (88.2%)	16 (84.2%)	49 (90.7%)
Drug withdrawal/ dose interruption	1 (12.5%)	0	0	3 (15.8%)	4 (7.4%)
Discontinued study • AE • Lost to follow-up • Other • Patient withdrew	0	0	2 (11.8%) • 0 • 1 (5.9%) • 0 • 1 (5.9%)	3 (15.8%) • 1 (5.3%) • 0 • 1 (5.3%) • 1 (5.3%)	5 (9.3%) • 1 (1.9%) • 1 (1.9%) • 1 (1.9%) • 2 (3.7%)

*Transplant was NOT a pre-specified part of the trial protocol, and only occurred at the investigators discretion if the possibility became available. †One patient did not receive a transplant following an infusion-related reaction (serious adverse event) with imlifidase that resulted in treatment and study discontinuation. AE: adverse event

These 54 patients received a variety of doses throughout these clinical studies, and these are summarised in Table 22. This table refers to the dose of each infusion, and so the patients who received two doses at 0.25mg/kg received a total dose of 0.50mg/kg. A single dose of 0.25mg/kg was the most commonly administered and was received by 39 patients (72.2%).

Table 22 Doses of imlifidase received by patients

Number of infusions	Dose administered in each infusion				
	Incomplete (n=2)	0.12mg/kg (n=3)	0.25mg/kg (n=44)	0.50mg/kg (n=5)	Total (n=54)
1	2*	0	39	5	46
2	0	3	5	0	8

*One patient in 13-HMedIdeS-02 had an incomplete dosing of imlifidase [redacted] and one patient in 15-HMedIdeS-06 had an incomplete dosing of imlifidase [redacted].

All 54 patients reported at least one AE and at least one treatment-emergent AE (TEAE; defined as an AE with onset up to 30 days after the last dose of imlifidase). A summary of these figures is included in Table 23. Adverse events considered related to imlifidase occurred in 37.0% of patients; a conservative approach was taken in

this regard, and if causality information was missing the event was assumed to be related to imlifidase.

Table 23 Summary of adverse events

Patients experiencing the following	Transplanted (n = 46)	Not transplanted (n = 8)	Total safety set (n = 54)
≥1 AE	46 (100.0%)	8 (100.0%)	54 (100.0%)
≥1 TEAE	46 (100.0%)	8 (100.0%)	54 (100.0%)
≥1 treatment-related AE	13 (28.3%)	7 (87.5%)	20 (37.0%)
Any mild AE	3 (6.5%)	3 (37.5%)	6 (11.1%)
Any moderate AE	3 (6.5%)	1 (12.5%)	4 (7.4%)
Any severe AE	5 (10.9%)	3 (37.5%)	8 (14.8%)
Any life-threatening AE	2 (4.3%)	0	2 (3.7%)
≥1 treatment-related TEAE	12 (26.1%)	7 (87.5%)	19 (35.1%)
Severe treatment-related TEAE (non-SAE)	3 (6.5%)	0	3 (5.6%)
Fatal AE	0	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

B.2.10.2 Treatment-related adverse events

A summary of all the adverse events determined to be treatment-related are summarised in Table 24. These results are split into TEAE and post-TEAE (defined as an AE with onset beyond 30 days after the last dose of imlifidase). Most of these adverse events occurred at low frequencies and were experienced by only one or two patients. An increased risk of infection is possible when IgG levels are compromised as a result of imlifidase treatment. The risk of infection was managed through prophylactic antibiotics until IVIg was administered or IgG levels returned to acceptable values. Several different infections were reported within the AEs reported, but only pneumonia and urinary tract infections were reported by more than one patient.

Table 24 Summary of treatment-related adverse events

	TEAE (n = 54)	Post-TEAE (n = 54)	Total safety set (n = 54)
Total	**19 (35.2%)**	**4 (7.4%)**	**20 (37.0%)**
Raised aspartate aminotransferase	2 (3.7%)	–	2 (3.7%)
Headache	2 (3.7%)	–	2 (3.7%)
Pneumonia	1 (1.9%)	2 (3.7%)	3 (5.6%)
Urinary tract infection	3 (5.6%)	–	3 (5.6%)
Raised alanine aminotransferase	2 (3.7%)	–	2 (3.7%)
Dizziness postural	1 (1.9%)	–	1 (1.9%)
Flushing	2 (3.7%)	–	2 (3.7%)
Infusion-related reaction	2 (3.7%)	–	2 (3.7%)
Infusion site pain	2 (3.7%)	–	2 (3.7%)
Myalgia	2 (3.7%)	–	2 (3.7%)
Sepsis	2 (3.7%)	–	2 (3.7%)
Abdominal infection	–	1 (1.9%)	1 (1.9%)
Adenovirus infection	1 (1.9%)	–	1 (1.9%)
Anaemia	1 (1.9%)	–	1 (1.9%)
Raised blood phosphorus	1 (1.9%)	–	1 (1.9%)
Raised blood triglycerides	1 (1.9%)	–	1 (1.9%)
Catheter site infection	1 (1.9%)	–	1 (1.9%)
Dyspnoea	1 (1.9%)	–	1 (1.9%)
Escherichia test positive	1 (1.9%)	–	1 (1.9%)
Feeling hot	1 (1.9%)	–	1 (1.9%)
Hypertension	1 (1.9%)	–	1 (1.9%)
Hypotension	1 (1.9%)	–	1 (1.9%)
Infection	1 (1.9%)	–	1 (1.9%)
Influenza	1 (1.9%)	–	1 (1.9%)
Parvovirus infection	–	1 (1.9%)	1 (1.9%)
Postoperative wound infection	1 (1.9%)	–	1 (1.9%)
Rash	1 (1.9%)	–	1 (1.9%)
Scleral haemorrhage	1 (1.9%)	–	1 (1.9%)
Sinus tachycardia	1 (1.9%)	–	1 (1.9%)
Transplant rejection	1 (1.9%)	–	1 (1.9%)
Upper respiratory tract infection	1 (1.9%)	–	1 (1.9%)
Visual impairment	1 (1.9%)	–	1 (1.9%)
Wound infection	1 (1.9%)	–	1 (1.9%)

TEAE: treatment-emergent adverse event

B.2.10.3 Serious adverse events

At least one SAE was reported by 38 patients (70.4%), with a total of 112 SAEs reported. The SAEs reported by at least two patients are summarised in Table 25. The most common SAEs were transplant rejection (19 patients [35.2%]), urinary tract infection (5 patients [9.3%]), and increased blood creatinine (5 patients [9.3%]). It is important to highlight that transplantation-related events, such as graft rejection, are expected in some patients following kidney transplantation and that urinary tract infections are also associated with the underlying kidney disease and are common after kidney transplantation. Although the numbers are small, it can be seen that patients who received a transplant had a higher rate of SAEs, this implies that at least some of these events are likely to have been associated with the kidney transplant procedure rather than imlifidase treatment.

Table 25 Serious adverse events

	Transplant (n = 46)	No transplant (n = 8)	Total safety set (n = 54)
Total	[redacted]	[redacted]	**38 (70.4%)**
Transplant rejection	[redacted]	[redacted]	19 (35.2%)
Urinary tract infection	[redacted]	[redacted]	5 (9.3%)
Raised creatinine	[redacted]	[redacted]	5 (9.3%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

A further analysis was conducted on treatment-related SAEs, of which there were twelve reported in 11 patients (20.4%); these are summarised in Table 26. The treatment-related SAEs reported in multiple patients were pneumonia (3 patients [5.6%]) and sepsis (2 patients [3.7%]). Overall, 9 of the 12 treatment-related SAEs were infections.

Table 26 Treatment-related serious adverse events

	Total safety set (n = 54)
Total	**11 (20.4%)**
Infections and infestations	*8 (14.8%)*
Abdominal infection	1 (1.9%)
Catheter site infection	1 (1.9%)
Parvovirus infection	1 (1.9%)
Pneumonia	3 (5.6%)
Sepsis	2 (3.7%)
Upper respiratory tract infection	1 (1.9%)
Immune system disorders	*1 (1.9%)*
Transplant rejection	1 (1.9%)
Musculoskeletal and connective tissue disorders	*1 (1.9%)*
Myalgia	1 (1.9%)
Injury, poisoning and procedural complications	*1 (1.9%)*
Infusion related reaction	1 (1.9%)

Lines in italics within the tables are System Organ Classes, with the individual events within that class listed in the lines below.

B.2.10.4 Adverse events of special interest

Imlifidase belongs to a new therapeutic class (IgG endopeptidases) and it is, therefore, difficult to define an expected risk profile. However, based on the mode of action of imlifidase (which leads to a transient major reduction in serum IgG levels) it would be expected that the AEs from this treatment would resemble the clinical picture of IgG deficiency. This insight was combined with observed safety findings and expected AEs due to the mode of administration of imlifidase, to identify the following as AEs of special interest within the clinical trial protocols for imlifidase: severe or serious infections, infusion-related reactions, and severe or serious myalgia. The incidence of these specific AEs are summarised in Table 27.

Table 27 Incidence of adverse events of special interest

	Number of patients (%) (n = 54)
Severe or serious infection	9 (16.7)
Infusion-related reactions	3 (5.6)
Severe or serious myalgia	1 (1.9)

Based on the mode of action of imlifidase, there is potentially an increased risk of infections whilst IgG levels are compromised. This risk is especially pertinent in a population that has undergone surgery, is hospitalised, and will then be receiving immunosuppressive treatment as part of the standard of care for their transplant. IgG levels start to return 1 to 2 weeks after treatment with imlifidase, but may be suppressed for up to approximately 1 month. As IgM and IgA remain unaffected by imlifidase treatment, a primary and secondary immune response to an infection is possible. In addition, to mitigate the risk of infections, prophylactic antibiotics covering respiratory infections were given in the clinical studies and the SAE data show that these types of infection were only experienced by a small number of patients. However, a high risk of infection remains in these patients, with 17% experiencing a severe or serious infection. It is also highly likely that the underlying disease, the surgery, and the immunosuppressive treatment may have increased the risk of severe or serious infections.

As with other biologic agents administered intravenously, infusion-related reactions may occur during imlifidase infusion. For this analysis of AE of special interest, only events of infusion-related reactions occurring from start of imlifidase infusion to start of transplantation (or within 48 hours of imlifidase infusion in non-transplanted patients) were included. To mitigate the risk of infusion-related reactions, glucocorticoids and antihistamines were given prior to imlifidase dosing. Overall, there were 4 patients (6%) who experienced infusion-related reactions. [redacted]. The overall frequency of infusion-related reactions with imlifidase was in the low range compared to other reported frequencies of these reactions.

Myalgia is an AE that has been reported during treatment with other biologic treatments, and so episodes of severe or serious myalgia were considered for the analysis of AEs of special interest. Severe or serious myalgia was reported by only one patient (2%), who experienced ‘severe or serious myalgia’ two days after a second dose of 0.25mg/kg imlifidase, which was assessed as related to imlifidase and did not resolve during the study. [redacted]

[redacted]. Besides this patient, [redacted], no other cases of severe or serious myalgia were reported during clinical trials of imlifidase.

B.2.10.5 Transplant-related events

Transplantation-related events, such as DGF and graft rejections, are expected after kidney transplantation, especially in recipients of deceased-donor organs and in subjects being transplanted for a second or subsequent time. It was important to consider whether imlifidase had an impact on these events. The data showed that there was no evidence that imlifidase had any adverse effect on the transplanted kidney.

Among the 46 transplant recipients during the clinical trials of imlifidase, 31 (67%) did not have any signs of AMR, while 15 (33%) had at least one episode of antibody-mediated changes. One of these was a non-IgG mediated hyper-acute rejection (potentially IgM mediated) that caused an immediate graft loss. Of the 14 remaining cases, eleven were identified by clinical signs and proven by biopsy and defined as active and/or chronic; three were identified at biopsy without any clinical signs and defined as subclinical. The majority of the AMR episodes occurred during the first six months after transplant and were resolved successfully. The frequency of AMR in patients treated with imlifidase is within the expected range of frequencies..

DGF presents as a suboptimal renal function immediately after kidney transplantation, defined as the need for dialysis within seven days of transplantation but that then resolves over time. DGF is a manifestation of acute kidney injury associated with the transplant process (*e.g.* ischemia, cold storage and reperfusion injuries). DGF was experienced by [redacted] in the imlifidase trials. Of these, kidney function was established within one week for [redacted] and within one month for a further [redacted]. The rate of DGF in patients treated with imlifidase is again comparable to that reported for other highly sensitised patients.

B.2.10.6 Death

No deaths were reported during the main period of the clinical trials of imlifidase. However, during longer-term follow-up of these patients, three deaths were reported between 6 months and a year after imlifidase treatment. None of these deaths were considered to be related to imlifidase or kidney malfunction.

B.2.10.7 Additional adverse event data

The literature review conducted as part of this appraisal also identified the Phase I study of imlifidase (11-HMedIdeS-01) as a source of additional safety data.[77] This study was conducted in healthy volunteers and so is less directly relevant to the population of interest. Therefore, this study is described in detail within Appendix F, where more detailed safety results are also included.

In 11-HMedIdeS-01, 77 AEs were observed in 24 of the 29 healthy subjects, with 39 being possibly or probably related to imlifidase (in 14 subjects). Among these 39 AEs, 35 were Grade 1. Four AEs were Grade 2 (all observed in one subject who experienced a probable infusion reaction, which resolved within 15 minutes after treatment with an antihistamine [2mg intravenous clemastine fumarate] and corticosteroids [8mg intravenous betamethasone]). The infusion reaction did not cause the imlifidase infusion to be interrupted. None of the SAEs caused a dose reduction or led to withdrawal of imlifidase. These safety data provide no additional safety concerns around imlifidase treatment.

B.2.11 Ongoing studies

An additional long-term follow-up study (17-HMedIdeS-14) for all patients transplanted in 13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06 is ongoing. This study may include up to 46 patients (all transplanted patients in the above studies) who will be assessed by kidney function, graft survival and patient survival for 5 years. It is known that 29 of the 46 patients transplanted in the feeder studies have been actively enrolled by the data cut-off date for this trial of [redacted]. It is expected that the final study visit will occur in Q4 2022, and the final study report is planned for completion in Q4 2023.

B.2.12 Innovation

Imlifidase is a highly innovative treatment that represents a step-change in the management of transplantation. Imlifidase is highly innovative in using a bacterial enzyme to specifically degrade human IgG to remove DSA that would otherwise prevent a transplant from being carried out. No other available treatments are able to rapidly and specifically remove IgG and thereby temporarily suppress all DSAs. Indeed, the innovative nature of imlifidase, and the unmet need in this area, led to imlifidase being granted eligibility to the PRIME scheme by EMA.[2]

The unmet need within highly sensitised patients arises primarily from these patients being unlikely to be transplanted and therefore spending far longer on dialysis waiting for a transplant.[15] In the UK, 98% of patients on the transplant list who have had a wait of at least 7 year are classified as highly sensitised (cRF ≥85%).[15] Transplant is the current gold standard treatment for patients with ESRD, and so the ability to provide these patients with access to this treatment option is a significant advance in therapy. Although there are other desensitisation protocols currently available, these are experimental treatments that are all unlicensed, of unproven efficacy, and generally require extended treatment periods making them suitable for living donor transplant only. Imlifidase is a step-change in therapy that provides a desensitisation treatment that is rapid and effective, and allows for the successful transplant of patients within the time window of a deceased donor organ who would have otherwise been unlikely to receive a transplant.

This ability to improve access to transplant for highly sensitised patients is particularly important from an equality point of view, as certain groups are currently particularly disadvantaged within the transplant system. Patients who are BAME currently have lower rates of transplant, and experience increased waiting times for a transplant. The use of imlifidase would allow for minority patients with a positive crossmatch who would otherwise not receive a transplant to do so. By doing so, this will help equalise access to transplant for this underserved patient group.

Women who have been pregnant have an increased risk of becoming highly sensitised due to their exposure to foetal antigens. This means that women are disproportionately likely to experience longer waiting times for a donor kidney. The

use of imlifidase would provide a new route for transplant in mothers, and, thereby, help equalise access to transplant across all patients.

These equality impacts cannot be captured within the economic model and so cannot be represented within the quality-adjusted life year (QALY) calculations. In addition, the full impact of dialysis can be challenging to capture within the economic model. Dialysis is an intensive treatment modality that requires significant time from patients. Over the long-term, dialysis is associated with a number of significant health problems. In addition, for those patients treated in dialysis centres, there is a large travel burden and also a potentially large burden on caregivers. Whilst reimbursed travel costs can be included within the economic model, the full burden imposed on the patient is very challenging to capture fully. Also, although an attempt has been made to incorporate the burden on caregivers through the modelling of a caregiver disutility, a lack of available data has made this challenging. There is, therefore, a likelihood that dialysis as modelled within the economic model does not capture the full burden and costs of dialysis. Also, as it is excluded from the NICE reference case, the modelling does not capture impacts on work productivity. Therefore, these impacts would not be fully reflected within the QALY calculations and can be considered conservative for imlifidase.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Efficacy of imlifidase at reducing DSAs

The clinical trial results show that imlifidase is a rapid and efficacious treatment to eliminate DSAs from the blood of highly sensitised patients. Imlifidase was able to induce a crossmatch conversion in all treated patients. Imlifidase can therefore enable transplantation in a small group of patients who otherwise are unlikely to receive a transplant. Imlifidase was able to induce a crossmatch conversion within a few hours (and mostly with a single dose), such that patients were considered eligible for transplantation. The rapid efficacy of imlifidase is important as it allows a transplant to proceed within the small window available for a deceased donor transplant. The clinical data confirm that anti-HLA antibody levels rapidly declined to

acceptable levels following imlifidase treatment and remained at this level until around seven days post-transplant.

The trials of imlifidase have also demonstrated its efficacy within a variety of different transplant treatment protocols in a number of countries around the world. This gives confidence that the efficacy of imlifidase is not impacted by different adjuvant treatments administered during the transplantation process.

B.2.13.2 Transplant outcomes

The clinical data show that in all cases, transplants were able to be undertaken following crossmatch conversion with imlifidase. These transplants were successful in almost all cases at the end of the six month primary study period and a functional kidney graft resulted. DGF was observed in a number of patients, but this resolved successfully to lead to functional graft outcomes. In functional grafts, the eGFR was in line with levels seen within UK patients that form the UKRR.[9] Graft survival was also broadly in line with expectations based on other kidney transplants and UK data from the NHSBT Annual Report.[15] These data give confidence that imlifidase leads to a successful transplant outcome.

B.2.13.3 Safety of imlifidase

Patients undergoing a transplant are known to experience a number of AEs related to the procedure and with the associated immunosuppressive regimens required. The studies of imlifidase reported that AEs judged to be treatment-related affected only 37% of patients. In addition, most of these AEs were mild to moderate in severity. The incidence of treatment-related SAEs, most commonly infections, was low and affected only 20% of patients, which was as expected due to the immunosuppressive nature of imlifidase, and the other immunosuppressive regimens these patients are provided to allow transplantation. There were no deaths during the trials of imlifidase and three deaths were reported during additional follow-up (all unrelated to imlifidase or kidney malfunction). In addition, the incidence of transplant-related events was in line with rates expected in similar patient types undergoing transplant. Therefore, the overall safety profile of imlifidase was considered acceptable in relation to the severity of the indication.

B.2.13.4 Strengths and weaknesses

The imlifidase studies were conducted in a methodologically robust manner, with the non-randomised, non-controlled design necessary for ethical reasons. The size of the studies was limited by the small patient population for this orphan indication, but was of a good size when considering these limiting factors. A quality assessment of these trials found a moderate risk of bias in the confounding domain (the risk of bias was low across all other domains). This was expected based on the study design and there is no reported confounding factors for the primary endpoints of these studies (ability of imlifidase to decrease in anti-HLA antibodies to make the patient suitable for kidney transplantation). The studies recruited only confirmed highly sensitised patients who had proven high levels of anti-HLA antibodies and there are no known natural mechanisms that lead to a spontaneous reduction in anti-HLA antibodies of the order of magnitude seen within the clinical trials. Whilst this cannot guarantee that other, unknown mechanisms have influenced the results, they provide a reassurance of the internal validity of the studies. Overall, the internal validity of these studies can be seen to be strong, but with some minor limitations expected based on the necessary study design.

The external validity of these studies and their ability to be generalised to the UK patient population is strong. An analysis of the most relevant patients to UK practice was presented as part of this study (highly sensitised patients who are considered unlikely to receive a transplant that received a deceased donor transplant). The characteristics of these patients are comparable to those expected within the UK patient population. The primary outcomes assessed in these studies primarily focussed on the ability of imlifidase to reduce DSA and to lead to acceptable antibody levels for a transplant to proceed. Data have also been collected to show that there are no adverse effects on the transplant from imlifidase treatment. As transplant is the accepted gold standard treatment for ESRD patients, and the risks associated with this procedure are well known, the ability of imlifidase to allow a transplant to be undertaken whilst not negatively affecting the transplant are the most relevant outcomes. From a patient point of view, the ability to receive a transplant in this patient group, where historically there has been very little hope of transplant due to their sensitisation, is a key endpoint.

Another aspect that must be considered when assessing the generalisability of these results to UK is the transplant treatment protocols used. None of the clinical trial evidence has been collected within the UK, and as the trials incorporated imlifidase into local protocols at the study locations means that these protocols do not exactly match those used within UK practice. The results published in Jordan et al. (2017) also showed some significant differences in antibody results between US and Swedish patients,[5] which can likely be attributed to some of these protocol differences. However, whilst this variation in protocols during the trials of imlifidase did lead to some discernible differences in the antibody response, the primary outcomes and key efficacy measures demonstrated the efficacy of imlifidase within all the protocols used. This demonstrates that the adjuvant treatments related to transplantation do not have a major impact on the efficacy of imlifidase and therefore give confidence that the results are generalisable to UK transplant practice.

B.2.13.5 End-of-life criteria

Imlifidase does not meet the end-of-life criteria, as although long-term dialysis can lead to an increased mortality, there is no evidence that the patients for which imlifidase is indicated have a life expectancy of less than 24 months.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

Appendix G describes the systematic literature review conducted in order to identify relevant cost-effectiveness studies. This review did not identify any studies that investigated the cost-effectiveness of imlifidase or dialysis in a population relevant to this technology appraisal. No cost-effectiveness studies in similar populations were found that could directly inform this submission.

B.3.2 Economic analysis

No previous cost-effectiveness studies were available to directly inform the economic analysis. Therefore, a *de novo* model was developed to address the economic case for imlifidase versus dialysis.

No comparative data are available for imlifidase (or kidney transplant) versus dialysis in highly sensitised patients. Therefore, a variety of data sources have been required to assemble the data required for this model.

B.3.2.1 Patient population

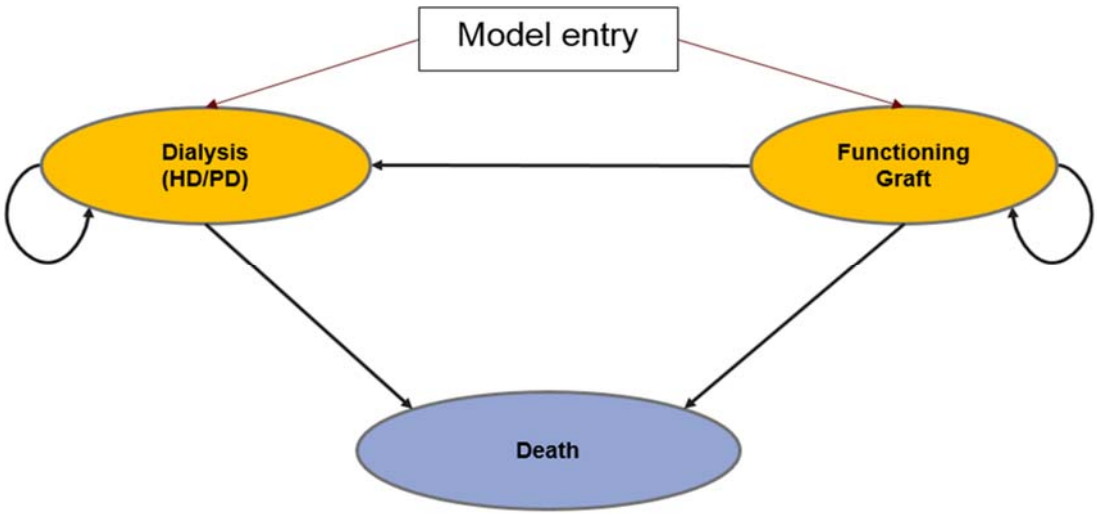
The patient population being assessed within this economic evaluation are those patients that fall within the licensed indication for imlifidase. This can be summarised as adults with chronic kidney disease awaiting a kidney transplant from a donor, who are highly sensitised with HLA, have a positive crossmatch with the donor, and are unlikely to be transplanted under the available KOS (after consideration of the revised version of the KOS).

This patient population is more specific than that documented in the scope and decision problem, but it better reflects the marketing authorisation of imlifidase. This population is also more specific than the patients included within the clinical trials of imlifidase. Due to the requirements of the model, in some cases data from slightly different populations has been required to be used. Wherever such data have been used, appropriate justifications have been given. This model has been designed to optimally reflect the population of interest using the best data available.

B.3.2.2 Model structure

A standard, cohort-simulation, Markov model was developed using Microsoft Excel® to assess costs and effects, life years (LYs) and QALYs of imlifidase with kidney transplant and dialysis in a cohort of adult highly sensitised patients on the deceased donor transplant list. Figure 8 provides a diagrammatic representation of the model structure and health states. This model structure matches the clinical pathway of care, where dialysis and transplant are the two RRT options available for these patients. The model has a 6-month cycle duration, and a half-cycle correction applied.

Figure 8 Model diagram



HD: haemodialysis; PD: peritoneal dialysis

The model includes 3 health states: 1) on dialysis (HD/haemofiltration or PD); 2) functioning graft; and 3) death. As the target population considers those highly sensitised patients that are unlikely to be transplanted under the available KOS, dialysis was considered to be the only relevant comparator. Patients enter the model and either receive dialysis (which they continue receiving until death) or they are treated with imlifidase and receive a negative crossmatched kidney transplant. Patients who undergo transplant remain in the 'functioning graft' health state until they lose their graft and return to dialysis or die. Death is an absorbing state.

No previous appraisals were available to inform the economic analysis for this appraisal. The relevant economic analysis features used in the current appraisal can be found in Table 28.

Table 28 Features of the economic analysis

	Previous appraisal	Current appraisal	
Factor	**TAXXX**	**Chosen values**	**Justification**
Time horizon	N/A	Lifetime (6-month cycle duration; half-cycle correction applied)	These patients have a chronic condition that they will have for the rest of their lives. Therefore, it is reasonable to conclude that a lifetime horizon is most suitable in this situation.
Treatment waning effect?	N/A	Not included	A treatment waning effect has not been included, as imlifidase is a one-off treatment to desensitise a patient to enable a kidney transplantation within 24 hours of administration. Therefore, it is not possible to include one for imlifidase.
Source of utilities	N/A	EQ-5D-5L data from a UK-specific study of dialysis and kidney transplant patient	No specific utility data are available for imlifidase. Utility data for the specific population considered in this appraisal were also not available and, therefore, the best available published evidence has been sourced and used.
Source of costs	N/A	BNF, eMIT, NHS Reference Costs	Standard sources of NHS costs, and matches NICE reference case.
Resource use	N/A	Published data	Relevant resource use data was collected from identified published data and was verified by clinical experts.
Health effects measure	N/A	QALYs	NICE reference case
Discount rate for costs and QALYs	N/A	3.5% per year	NICE reference case
Perspective	N/A	NHS/PSS	NICE reference case

BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool

B.3.2.3 Intervention technology and comparators

The intervention of interest in this economic analysis is imlifidase, which is used to enable a kidney transplant from a deceased donor. Imlifidase is offered within 24

hours prior to a transplant in order to desensitise chronic kidney disease patients who are highly sensitised and have a positive crossmatch to an available deceased donor kidney. In patients that do not achieve a crossmatch conversion, there is the ability to administer a second dose of imlifidase.

The comparator treatment in this economic analysis is dialysis. Long-term dialysis is the only available alternative treatment option for these highly sensitised patients, who have a positive crossmatch and are contraindicated for transplant. Dialysis in these patients is assumed to continue until death.

B.3.3 Clinical parameters and variables

Clinical parameters and variables used within this economic analysis were based on the trial data from the pivotal trials for imlifidase (13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06; see Section B.2 for further details). As well as direct trial data, other sources were utilised where necessary (for example in the extrapolation of data past the observed clinical trial periods).

Graft survival and patient survival have been used to provide the main clinical efficacy outcomes for the functioning graft health state in the model. It was assumed (based on the clinical trial data) that crossmatch conversion (and hence transplant) occurred in 100% of treated patients. Patients whose graft becomes non-functioning transition to the dialysis health state (as it is assumed that they will require dialysis in this situation). Dialysis survival is used as the clinical measure within the dialysis health state in the model. Patients that die transition to the death health state within the model. Further details on all of these clinical data are given in the following sections.

B.3.3.1 Baseline characteristics

Table 29 summarises the baseline characteristics used in the model. The characteristics of the simulated patient cohort at model entry were based on the baseline characteristics of the HLA incompatible renal transplants (n=522) on the UK National Registry between 1 January 2001 and 31 December 2012.[78] This was taken as the most relevant baseline characteristic data that could be found to represent highly sensitised patients, a group that has differences in demographics to a more

general transplant population (one reason for this is the overabundance of previously pregnant women in this highly sensitised group).

Table 29 Baseline model cohort characteristics

	Base case	SE	95% CI
Initial age (years)	45	4.5	36–54
Proportion of females (%)	60	6.0	48.1–71.3

CI: confidence interval; SE: standard error

B.3.3.2 Graft survival

Three approaches have been used to predict graft survival over time in patients treated with imlifidase, these were: the interactive Box (iBox) model, extrapolation based on all imlifidase patients, and extrapolation based on the 'unlikely to be transplanted' patient group (as presented in Section B.2.8.2). The iBox model is used as the base case approach; each approach is described in detail below.

B.3.3.2.1 iBox

The iBox is a tool for predicting the risk of kidney transplant loss based on artificial intelligence. The iBox was developed by Prof Alexandre Loupy and his team, in collaboration with centres across the world, to address the need to predict long-term kidney allograft survival.[79]

The iBox 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 4000 kidney transplant recipients from four French transplant centres (two centres in Paris, one in Suresnes and one in Toulouse) who underwent a kidney transplant between 2005 and 2014.[79] Thirty-two prognostic factors were analysed, including donor and recipient parameters, as well as parameters collected at the time of evaluation within the standard of care terms of follow-up (creatinine, proteinuria, DSA and eGFR measurement, and biopsy results).[79]

All 32 parameters were evaluated as determinants of allograft survival in a univariate Cox analysis and in a multivariate Cox model in which eight parameters were identified as independently associated with allograft loss.[79] These eight parameters are: post-transplant evaluation date; creatinine clearance; proteinuria; DSA;

histological parameters (interstitial fibrosis and tubular atrophy; microcirculation inflammation; interstitial inflammation and tubulitis); and transplant glomerulopathy.[79] The internal validity of the final model was confirmed by using a bootstrap procedure, which involved generating 1000 datasets derived from resampling the original dataset.[79] The accuracy of the prediction model was assessed on the basis of its discrimination ability and calibration performance.[79] The C-index of the iBox model was 0.81 (95% CI 0.79–0.83), which is considered good for a predictive model (a C-index of 1 would mean that each allograft loss is correctly predicted by the model, whereas a C-index of 0.5 would indicate that the model is non-discriminatory).[79] 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.[79] Finally, the accuracy of the iBox risk score in predicting long term allograft loss was further validated in three randomised controlled trials.[79] The iBox can, therefore, be seen to be an integrative, accurate, and readily implementable risk prediction score for kidney allograft failure, which shows generalisability across centres worldwide and common clinical scenarios. In addition, iBox has been validated in HLA incompatible patients, which are an equivalent patient group to that utilised here. This, therefore, provides a strong basis for producing extrapolated graft survival data for this economic model.

The imlifidase dataset analysed by the iBox model consisted of [redacted] patients with available histological data, eGFR, and DSA information. These patients were selected from the clinical trials of imlifidase based on the presence of the required data and were not selected for other reasons. Among these patients, [redacted] had no proteinuria evaluation, which is a key continuity marker for evaluation, and iBox evaluation was, therefore, not able to be performed for these patients. Therefore, [redacted] imlifidase patients were analysed using the iBox graft survival prediction tool. The iBox evaluation was performed at 6 months post-transplant, if possible, or at another earlier time point. This patient group was used as it consisted of the only imlifidase patients for whom the iBox analysis could be run. It is considered that these results are representative of the patient population of interest and the strengths of using the

validated iBox system were judged to outweigh the fact that the direct population of interest could not be evaluated using this method. The impact of this assumption is explored through sensitivity analyses conducted using other extrapolation methods.

Table 30 summarises the iBox graft survival prediction results. The iBox survival predictions were performed on patients with a functioning graft at 6 months (the evaluation period). At 6 months, the observed values of the independent predictors of survival were used as inputs to the iBox model. The predictions of iBox are based after this evaluation period and, hence, the one-year graft survival estimate post-evaluation from the iBox model represents 18 months post-transplant. Subsequently, the two-year graft survival estimate represents 30 months post-transplant, and so on.

Table 30 Graft survival post-evaluation prediction results from iBox

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

The iBox data have been used as the base case for the model as it provides the most robust data for prediction of graft survival over the longer term. In the model, graft survival estimates for the first 6 months are based on the observed imlifidase data from the 'unlikely to be transplanted' group. This allows the most relevant data to be used within the model. Since the iBox graft survival predictions do not take into account graft loss that occurs between transplant and 6 months, these values were multiplied by the proportion of patients with a functioning graft at 6 months (first cycle of the model). [redacted] percent ([redacted]%) of these patients had a functioning graft at 6 months. Applying the iBox predicted graft survival at one year ([redacted]%), [redacted]% of the patients ([redacted]% * [redacted]%) who entered the model will still have a graft at cycle 3 (18 months post-transplant). Table 31 shows the graft survival used in the model derived

from the survival at 6 months in the observed data and the iBox survival predictions at each year.

Table 31 Model graft survival

Model Cycle (6 months)	Years Post-Transplant	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 figures from Table 31 were fitted with parametric functions, and the extrapolations from the exponential, Weibull, log-normal, and log-logistic are shown against the iBox predictions in Figure 9.

Figure 9 iBox survival predictions and extrapolation

[redacted]

All functions appear plausible at visual inspection. The log-logistic and the log-normal are very similar and provide the most optimistic predictions. The Weibull function presented the best fit as it was associated with the smallest sum of least squared. In addition, it was considered a relatively conservative choice as the log-logistic and log-normal both resulted in higher long-term survival extrapolation. The Weibull function was used to calculate the probability of graft loss at each cycle over the lifetime of the model (beyond the 10.5 years based on the iBox data). The predicted graft survival and extrapolation were reviewed and considered reasonable by UK nephrologists and pharmacists participating in a virtual advisory board meeting that took place in June 2020.

B.3.3.2.2 All imlifidase patients

Graft survival using data from all imlifidase patients studied within the trials has also been analysed. These data offer the largest pool of patients treated with imlifidase, which provides the next most robust data for imlifidase. These data represent all the currently available evidence of efficacy for imlifidase following transplant, and, thus, should be seen to provide more robust results than any subgroups within this population. The reasoning being that, as more patients are included within the analysis, these data will be more tolerant to any outliers within the data than a smaller cut of the data would be, and, thus should provide more accurate results for graft survival.

Death censored graft survival using data from all 46 patients studied within the imlifidase clinical trials who underwent a kidney transplant showed that [redacted]% of the patients had a functioning graft at 6 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. These observed graft survival results were fitted with parametric functions (exponential, Weibull, log-normal, and log-logistic). The exponential function was the best fit according to the Akaike Information Criterion (AIC), and the Bayesian information Criterion (BIC) goodness fit of measures. Table 32 summarises the AIC and BIC extrapolation scores.

Table 32 Graft survival extrapolation AIC and BIC scores for all imlifidase group

Model	AIC	BIC
Exponential	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

AIC: Akaike Information Criterion; BIC: Bayesian information Criterion

The observed graft survival extrapolations are shown in the graph below (Figure 10). Visual inspection suggests that the results produced by the Weibull and the exponential are the most conservative. The exponential function was, therefore, chosen for the long-term survival estimates of this dataset, and is included in a scenario analysis in the model.

Figure 10 All imlifidase graft survival extrapolation

[redacted]

B.3.3.2.3 Imlifidase patients in 'unlikely to be transplanted' group

The 'unlikely to be transplanted' group offers the closest match to the patients suitable for imlifidase under its licensed indication, and was the focus of the main efficacy data presented in Section B.2.8.2. This scenario utilises data from a subset of the all imlifidase patient group, and due to the small numbers of patients available for analysis in this group, is considered a less robust analysis than the others

presented above. However, as this group represents the most directly relevant data for this appraisal these data have been considered for use as a scenario analysis.

The observed data in this group has been extrapolated over the full time horizon of the cost-effectiveness model using parametric functions (exponential, Weibull, log-normal, and log-logistic). The exponential distribution was the best fit according to the AIC and BIC criteria as shown in Table 33.

Table 33 Graft survival extrapolation AIC and BIC scores for 'unlikely to be transplanted' group

Model	AIC	BIC
Exponential	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

AIC: Akaike Information Criterion; BIC: Bayesian information Criterion

The different extrapolations are shown in Figure 11. The exponential and log-logistic predictions reflect the mid-range estimates, while the log-normal predicts the most optimistic results, and the Weibull the most conservative. The exponential function was, therefore, chosen for the long-term survival estimates of this dataset, and is included in a scenario analysis in the model.

Figure 11 'Unlikely to be transplanted' graft survival extrapolation

B.3.3.2.4 Comparison of the survival scenarios with the UK graft survival

Figure 12 shows the graft survival extrapolations for the three survival scenarios explored above (i.e. iBox results, all imlifidase group, and 'unlikely to be transplanted' group). This graph shows these graft survival estimates in comparison with the overall graft survival based on UK data over 10 years from the NHSBT Annual Report.[15] These data show that the three scenarios included within this economic model give predictions that are quite similar, with predictions produced by iBox, the input for the base case, being the most conservative of the three. These graft survival predictions are below those of the overall UK graft survival, which is not unexpected as these analyses are focussed on a group of highly sensitised patients. Without imlifidase, these patients would be unlikely to receive a transplant, or would only be able to have an incompatible transplant which would have lower graft survival.

Figure 12 Graft survival in comparison to overall UK graft survival

UTT: unlikely to be transplanted.

B.3.3.3 Transplant patient survival

B.3.3.3.1 All imlifidase patients

The patient survival input for the model uses the data from all imlifidase patients studied within the trials. These data offer the largest pool of patients treated with imlifidase and provides the most robust data available for imlifidase. These data represent all the currently available evidence of efficacy for imlifidase following transplant, and, thus, should be seen to provide more robust results than any subgroups within this population.

In this all imlifidase population, [redacted]% of patients were alive at 6 months after transplant. At the end of the first year, [redacted]% of patients were alive and this proportion remained stable through the rest of the data currently available. These patient survival results were fitted with parametric functions (exponential, Weibull, log-normal, and log-logistic). The exponential distribution was considered the best fit based on the AIC and BIC criteria, as shown in Table 34.

Table 34 Patient survival extrapolation AIC and BIC scores in all imlifidase group

Model	AIC	BIC
Exponential	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

AIC: Akaike Information Criterion; BIC: Bayesian information Criterion

Figure 13 shows the different extrapolations for patient survival in the model. The exponential distribution was the most conservative as it leads to lower survival predictions. The all imlifidase population was selected for the base case as it represented the most robust dataset, and the exponential function was used for the extrapolations of these results.

Figure 13 All imlifidase patient survival extrapolation

B.3.3.3.2 Imlifidase patients defined as highly unlikely to be transplanted

The ‘unlikely to be transplanted’ group offer the closest match to the patients suitable for imlifidase under its licensed indication. However, this utilises data from small numbers of patients, making this analysis less robust. The impact of the small group size on this analysis is outlined by the fact that the results in this group are based on three recorded deaths (none of which were determined to be related to imlifidase or kidney malfunction). In addition, no other deaths were recorded within the wider imlifidase treated group, showing that these results are potentially being influenced by the small group size. Therefore, although this group represents the most directly relevant data for this appraisal, these data have been considered for use as a scenario analysis.

The observed patient survival results were fitted with parametric functions (exponential, Weibull, log-normal, and log-logistic). The exponential distribution was considered the best fit based on the AIC and BIC criteria, as shown in Table 35.

Table 35 Patient survival extrapolation AIC and BIC scores for 'unlikely to be transplanted' group

Model	AIC	BIC
Exponential	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

AIC: Akaike Information Criterion; BIC: Bayesian information Criterion

Figure 14 shows the patient survival extrapolation for the 'unlikely to be transplanted' group. As with graft survival, the 'unlikely to be transplanted' population is the least robust of the populations considered as it includes the smallest number of patients, and the exponential function was used for the extrapolations of these results. As such, it was not selected for the model base case, but was explored as a scenario analysis.

Figure 14 Unlikely to be transplanted patient survival extrapolation

[redacted]

B.3.3.3.3 Comparison of the predictions of the two patient survival scenarios of the model with other sources

Figure 15 shows the patient survival extrapolations utilised in the model (all imlifidase group and 'unlikely to be transplanted' group results) in comparison with overall patient survival in UK based on the NHSBT Annual Report,[15] and with the

overall patient survival of HLA incompatible transplants (both living and deceased donor) from the UK National Registry.[78]

There is an important difference in data handling between that used in the model and the other sources considered here.[15,78] Within the imlifidase populations, patients were censored when they lost their graft, and, hence, survival with a functioning graft is considered. This matches how these data were collected within the clinical trials of imlifidase and match the model requirements (as once patients lose their graft they move to the dialysis health state where they are subject to the mortality rates based on that health state). In contrast, the data from NHSBT and UK National Registry of Incompatible Renal Transplantation both consider overall survival (i.e. patients are followed whether they lose their graft or not).[15,78] As a result, these curves show survival rates that are lower than that they would be if only survival with a functioning graft was included. These data show that the all imlifidase patient group follows a similar survival curve compared to the comparator data.[15,78] The extrapolation of the 'unlikely to be transplanted' population shows a lower patient survival estimate, but this is strongly influenced by the small group size of this population, making this estimate less reliable.

Figure 15 Patient survival in comparison to other UK survival data

DBD: donation after brain death; DD: deceased donor; HLAi: human leukocyte antigen incompatible; LD: living donor; UTT: unlikely to be transplanted.

B.3.3.4 Dialysis survival

Data for dialysis survival were sourced from the UKRR. Within the UKRR Annual report, data were produced showing the relative survival of patients receiving RRT in comparison to the general population.[9] A data request was made to UKRR to provide equivalent survival data specific to dialysis patients.[80] This provided a relative risk of death in 2018 for the UKRR dialysis population in comparison to the overall UK population split by five year bands. These relative risks were applied to the mortality calculated from the UK life tables based on the age and gender of patients within the model.[81] The relative risk of death in the dialysis population by age group is summarised in Table 36

This approach to modelling mortality in dialysis patients was taken from Jones-Hughes 2016.[82] It should be noted that this report by Jones-Hughes was developed during a previous NICE appraisal of immunosuppressive therapies for kidney transplant.[82] Whilst this appraisal had very different aims to the current appraisal (and so was not identified as a relevant cost-effectiveness study through the literature review), it does provide an outline of how the modelling of kidney transplantation has been considered previously by NICE.

Table 36 Relative risk of death for dialysis patients

UKRR 2018 dialysis population relative risk of death*	Base case	SE	95% CI
Age: 35–39	62.4	1.2	46.2–84.3
Age: 40–44	59.2	1.1	47.9–73.2
Age: 45–49	38.0	1.1	32.1–44.9
Age: 50–54	34.4	1.1	30.4–38.9
Age: 55–59	23.4	1.1	21.0–26.1
Age: 60–64	19.8	1.0	18.2–21.6
Age: 65–69	17.0	1.0	15.9–18.2
Age: 70–74	11.1	1.0	10.5–11.8
Age: 75–79	6.9	1.0	6.6–7.2
Age: 80–84	5.0	1.0	4.8–5.2
Age: 85+	2.7	1.0	2.6–2.8

*Data supplied by UK Renal Registry;[80] we thank all the UK renal centres for providing data to the UK Renal Registry; the views and opinions expressed herein are those of the authors and do not reflect the views of the UK Renal Registry or UK Renal Association. CI: confidence interval; SE: standard error

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality of life (HRQoL) data were not collected as part of the clinical trials for imlifidase. A longer term study is currently ongoing (17-HMedIdeS-14, see Section B.2.11), which is collecting HRQoL data from the imlifidase patients. However, it is expected that this study will be completed in Q4 2023.

B.3.4.2 Mapping

No mapping of utility was required or used in this model.

B.3.4.3 Health-related quality-of-life studies

The details of the systematic search conducted for identifying the relevant health-related quality of life data are included in Appendix H. These searches identified a total of two relevant publications that contained data on quality of life in patients with chronic kidney disease. However, no studies were found that reported HRQoL in the specific population of interest in this appraisal. It would be expected that utility values for highly sensitised patients would be significantly lower than that of the general chronic kidney disease population, owing to the fact that highly sensitised patients have very few options remaining and have been on dialysis significantly longer than the general chronic kidney disease populations reported in these studies.

B.3.4.4 Adverse reactions

B.3.4.4.1 Imlifidase-related adverse events

The model includes SAEs related to treatment with imlifidase that were reported during the clinical trials of this treatment. The decision to include only the treatment-related SAEs was supported by the fact that there are no comparators to imlifidase in the clinical trials. Table 37 summarises the imlifidase related SAEs that were utilised within the model (which are as reported in Section B.2.10.3). Note that there was also one SAE of transplant rejection that was considered as treatment-related; however, this was not included here as transplant rejections are already considered within the model as part of the graft survival data, and transplant-related adverse events are considered separately in the following section. These imlifidase-related

SAEs are used in the model with associated costs assigned to them; however, no data were available to include a disutility for these adverse events. The imlifidase-related SAEs were also assumed to occur only within the first cycle of the model, due to imlifidase only being administered immediately preceding transplant.

Table 37 Imlifidase-related serious adverse events

Imlifidase-related SAEs (Cycle 1)	Base case (%)	SE (%)	95% CI (%)
Pneumonia	5.6	0.6	4.5–6.7
Sepsis	3.7	0.4	3.0–4.5
Abdominal infection	1.9	0.2	1.5–2.2
Catheter site infection	1.9	0.2	1.5–2.2
Parvovirus infection	1.9	0.2	1.5–2.2
Upper respiratory tract infection	1.9	0.2	1.5–2.2
Infusion-related reaction	1.9	0.2	1.5–2.2
Myalgia	1.9	0.2	1.5–2.2
Transplant rejection	1.9	0.2	1.5–2.2

CI: confidence interval; SAE: serious adverse events; SE: standard error

B.3.4.4.2 Transplant-related adverse events

Transplant-related AEs, such as AMR and delayed graft function have been captured from the imlifidase trials and used within the model with associated costs. No AMR events were reported after the first year following transplant, and so AMR was included as an adverse event within the first two cycles of the model only. Details of the incidence of these events are summarised in Table 38.

Table 38 Transplant-related adverse events

Transplant AEs	Base case (%)	SE (%)	95% CI (%)
AMR (Cycle 1)	[redacted]	[redacted]	[redacted]
AMR (Cycle 2)	[redacted]	[redacted]	[redacted]
Delayed graft function (Cycle 1)	[redacted]	[redacted]	[redacted]

AMR: antibody-mediated rejection; AE: adverse event; CI: confidence interval; SE: standard error

B.3.4.4.3 Dialysis-related adverse events

The literature on the prevalence of adverse events for dialysis patients in the UK is limited, and so additional discussions were undertaken with a UK based clinical expert in dialysis to ensure that dialysis-related AEs were accurately modelled. The UKRR Annual Report provides a rate of peritonitis for PD patients as 45/100 patient

years.[9] This rate was converted into a per cycle probability and applied in the model to the PD patients. Discussions with UK based clinical expert in dialysis confirmed that the risk of peritonitis was elevated in the UK and was the most frequent dialysis-related AE for PD patients. According to the clinical expert consulted, the most frequent dialysis-related AE associated with HD is chest infection. On an annual base, the expert estimated that 8–10% of the HD patients on the transplant list would experience a chest infection that lead to hospitalisation. This is due to the high exposure of HD patients to airborne infections, because of the time spent in hospitals and clinics. Therefore, home dialysis and PD patients would be expected to be less impacted. An annual probability of 8% was converted into a rate per 6-month model cycle and was applied to the HD patients. Another, dialysis-related AE raised as relevant by the clinical expert was stenosis. Stenosis is unlikely to happen within the first two years, especially in younger patients, but may happen later over the course of the dialysis for approximately 10–12% of the patients on the transplant list over a 5-year period. The patients enter the model at the time they are offered a deceased donor kidney, and they are likely to spend time on the transplant list and on dialysis before being offered a kidney. Therefore, a 10% probability of stenosis over 5 years was converted into a per cycle probability and applied to the HD patients in the model. Table 39 summarises the rates of dialysis-related AEs that were used in the model.

Table 39 Dialysis-related adverse events

Dialysis AEs	Base case (%)	SE (%)	95% CI (%)
Peritonitis (PD patients only)	25.8	2.6	20.9–31.0
Chest infection (HD patients only)	4.1	0.4	3.3–4.9
Stenosis (HD patients only)	1.0	0.1	0.9–1.3

AE: adverse events; HD: haemodialysis; PD: peritoneal dialysis; SE: standard error

B.3.4.4.4 Health-condition related adverse events

Patients with ESRD are subject to many complications, irrespective of type of RRT, including cardiovascular events and infections. These adverse events were not included in the economic model as detailed published evidence relevant to the model was not identified. In addition, it would be expected that these events would have minimal impacts on the results of the economic analysis as they would be experienced equally by both arms of the comparison.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The model incorporates the approach outlined by Ara and Brazier 2010,[83] where the utilities for the general population per age and gender were used, adjusted with health state utility decrement.

B.3.4.5.1 Age- and gender-dependent utilities derived from the general population

The equation used to derive age- and gender-dependent health utilities was taken from Jones-Hughes 2016 (derived from the Health Survey for England 2012).[82] It should be noted that this report by Jones-Hughes was developed during a previous NICE appraisal of immunosuppressive therapies for kidney transplant.[82] Whilst this appraisal had very different aims to the current appraisal (and so was not identified as a relevant cost-effectiveness study through the literature review), it does provide an outline of how the modelling of kidney transplantation has been considered previously by NICE. For each cycle, a baseline utility is created using the following equation:

Equation 1: Age- and gender-dependent health utilities

$$\text{Utility} = 0.967981 - 0.001807 \times \text{age} - 0.00001 \times -\text{age}^2 + 0.023289 \times \text{male}$$

The model assumes 40% of patients are male. This proportion is multiplied by the male coefficient from the equation above and the age coefficients are multiplied by the corresponding age at each cycle, creating a general population utility that decreases in time as the patient ages.

B.3.4.5.2 Health state utility decrements

Two studies identified through the systematic searches were considered relevant to the population of interest and included in the model: Liem et al. (2008),[35] and Li et al. (2017).[36] Liem et al. (2008) is a meta-analysis of a number of HRQoL studies, and was considered the most appropriate source and so was utilised within the base case analysis.[35] The study by Liem et al. (2008) utilised a meta-analysis of relevant studies identified within a systematic literature review.[35] This study investigated a number of HRQoL measures and included 27 studies, 11 of which utilised the EQ-5D

(including almost 2500 patients).[35] This study also provided data on the age and gender of participants, alongside splitting data into those receiving transplant, HD and PD.[35] All of these match the requirements for this model, and so this extensive data can be seen to be an appropriate source for use in this model.

The study by Li et al. (2017) was a more recent study, which was focussed on the UK, but it had a number of factors which led it to be considered a less appropriate source.[36] The study by Li et al. (2017) utilised data from the Access to Transplantation and Transplant Outcome measure (ATTOM) study, which was a non-interventional, prospective, cohort study of patients aged less than 75 years starting dialysis, receiving a transplant and a similar number of matched patients active on the transplant waiting list, from all dialysis and transplant centres in the UK.[36] The quality of life measures were not a primary outcome from this study (which was primarily focussed on access to transplant), and so the study design did not prioritise these data (for example, a low completion rate was evident in the HRQoL survey).[36] However, the primary issue with this study was that it did not investigate the patient groups required for the model (transplant recipients and dialysis patients), with values reported for transplant recipients compared to waitlist patients.[36] The waitlist patients included many patients who were on the transplant list but were pre-dialysis, and, thus, do not reflect the population of dialysis patients as required for this model.[36] Also, waiting list patients selected for inclusion were matched to transplant recipients for the purpose of studying survival as an outcome, not for the measurement of health status.[36] Therefore, there may be some fundamental differences which mean that these populations are not necessarily suitable for comparison, such as matching time on dialysis in those within the waiting list and transplant groups.[36] Another key issue with the design of the study is that the questionnaire was administered by nursing staff in the hospital/caring environment. The use of carers to administer a questionnaire, whose focus is the effect of such care on life quality, is to be deprecated in all circumstances.[36] It is well known that patients have a tendency to try to please their carers (doctors, nurses etc.) when responding to questions and, thus, any assessments which are likely to be impacted by this tendency must be administered by an external agency. It is noteworthy that the highest response rate was amongst waiting list (dialysis) patients, where the

questionnaires were almost certainly conducted during their clinic attendance, by nursing staff that were part of the team trying to make the patient as comfortable as possible during their stay.[36] Ideally, the questionnaires should have been completed away from this environment, preferably at home or in a situation where their life perceptions were likely to be more objective. Additionally, this study had only 6 months of follow-up post-transplant (when effects of surgery may still be evident), did not report an average age (instead reported age groups that were not able to be mapped to the general population utilities), and utilised the EQ-5D-5L (results reported did not contain the granularity of information that would allow a conversion to the EQ-5D-3L, as recommended by NICE).[36] Therefore, Liem et al. (2008) was considered the most appropriate data source as it provided a meta-analysis that covered both dialysis and transplant patients, as required by this model, and was therefore used within the base case.[35] The data from Li et al. (2017) were included as a scenario analysis in the model.[36] These studies provide the best available data for the analysis of utilities within the health states in the model. However, neither study fully accounts for the detriment of being a highly sensitised patient on dialysis and, thus, can be considered to overestimate the utility values in the dialysis arm of the model.

The Liem et al. (2008) study summarised haemodialysis, peritoneal dialysis, and renal transplant patient utilities from a systematic literature search that identified 27 studies that met their inclusion criteria, including: reporting absolute utilities derived from the three-level EQ-5D (EQ-5D-3L; the measure pertinent for this model); at least one form of RRT specified as haemodialysis, peritoneal dialysis, or kidney transplant; data collected prospectively; and at least 10 patients per treatment group.[35] Table 40 reports the mean utility, mean age, and the proportion of males from this publication for haemodialysis, peritoneal dialysis, and transplant patients.[35] The final column (General population derived utility) contains the utilities that were derived using the equation above for the general population.

Table 40 Health state utilities (EQ-5D-3L) reported in Liem et al. (2008)[35]

Health state utilities	Utility	Age	Proportion of males	General population derived utility
Haemodialysis	0.560	60.4	0.58	0.836
Peritoneal dialysis	0.580	57.9	0.55	0.843
Functioning graft	0.810	51.4	0.60	0.863

The utility decrements were calculated by subtracting the reported utilities from the general population derived utilities for each health state. The resulting mean utility decrement was used as the base case in the model; these are presented along with the standard errors (SE) and the CIs in Table 41. For the dialysis health state, a weighted average was calculated using the proportion of patients on haemodialysis versus peritoneal dialysis, based on the patients on each modality reported in the UKRR 21st Annual Report.[80]

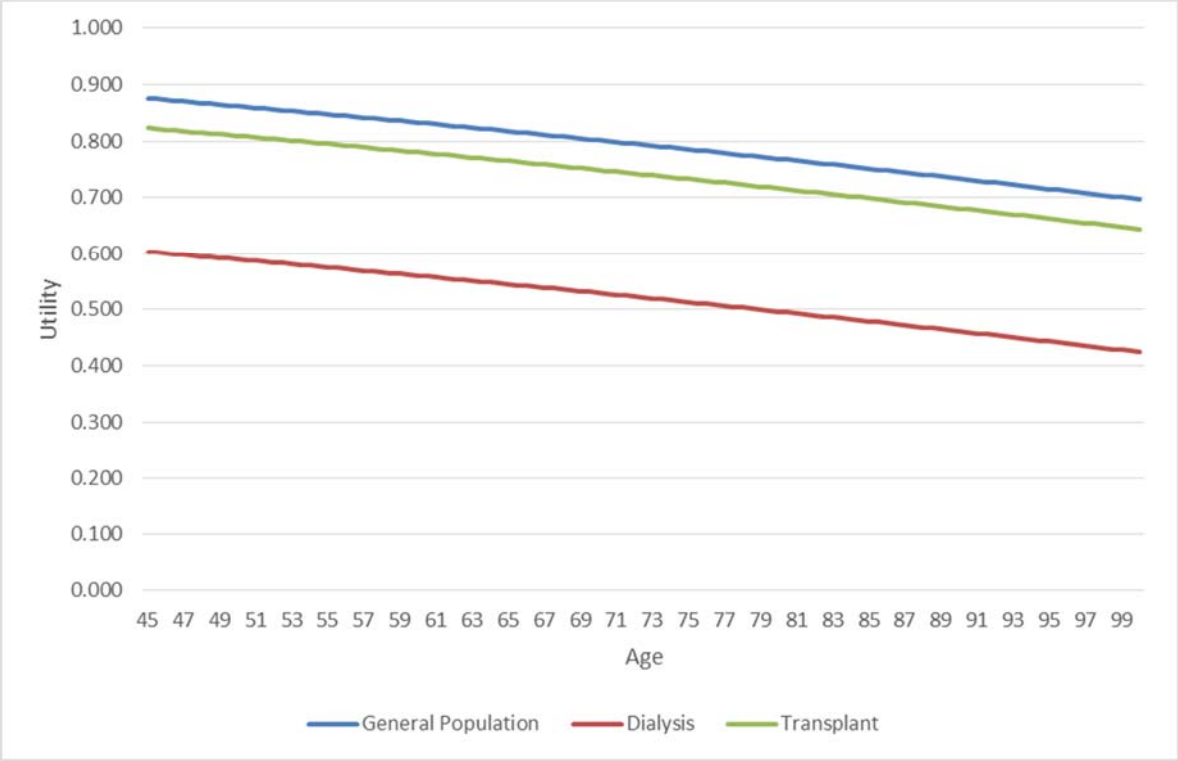
Table 41 Health state utility decrements utilised in model

Health state utility decrements	Base case value	SE	95% CI
Haemodialysis	0.276	0.033	0.216–0.346
Peritoneal dialysis	0.263	0.043	0.173–0.343
Functioning graft	0.053	0.046	-0.037–0.143

CI: confidence interval; SE: standard error

The health utilities by age as utilised in the model are presented in Figure 16.

Figure 16 Utility estimates by age as utilised in model



B.3.4.5.3 Age-dependent utility scenario analysis

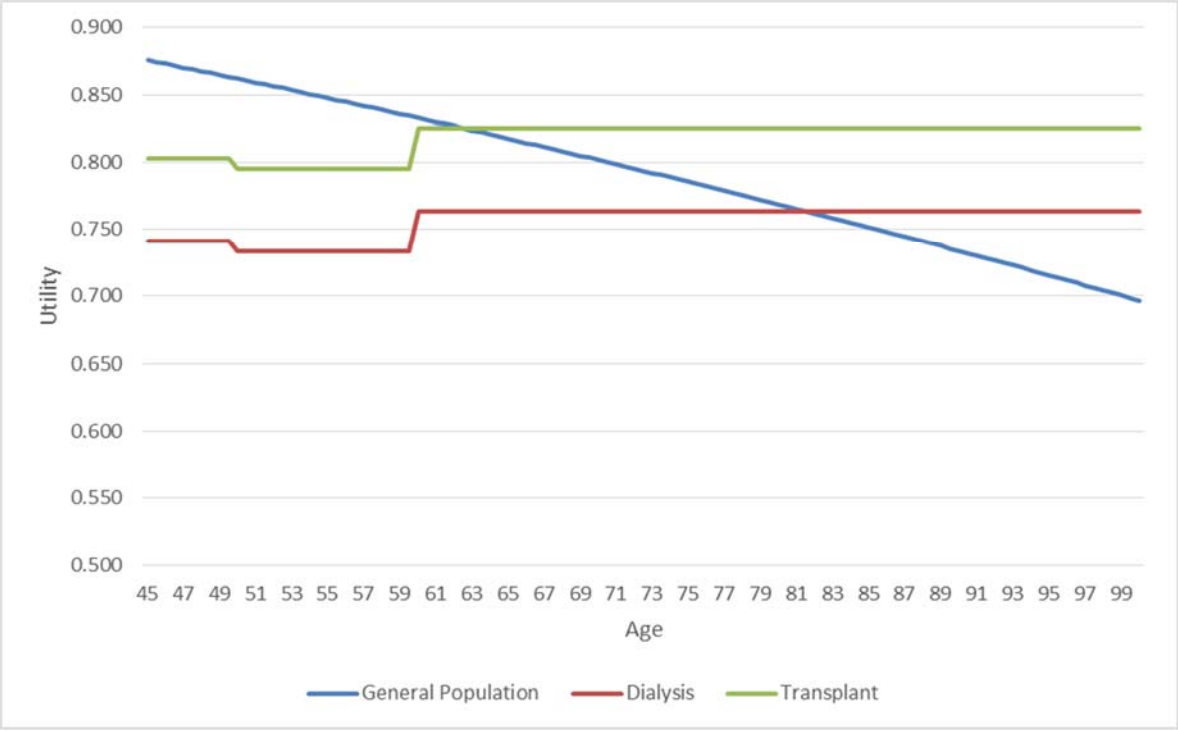
The publication by Li et al. (2017) evaluated health state utility values for a large sample of adult kidney transplant and waiting list patients (ages 18–75) in the UK.[36] A total of 2250 kidney transplant patients and 1959 waiting list patients (18–75 years) were assessed on the EQ-5D-5L value set for England.[36] Of these, 512 kidney transplant and 1704 waiting list patients were re-assessed after 6 months.[36] Li et al. (2017) reported a model that allowed for an age-group based utility.[36] Regression coefficients were used to derive utilities per age group for transplant and waiting list patients.[36] Table 42 summarises the derived utilities based on these coefficients.

Table 42 Health state utilities per age group and transplant status

Health state utilities	Age	Derived utilities
Waiting list	30–39	0.768
	40–49	0.765
	50–59	0.757
	>60	0.787
Transplant	30–39	0.821
	40–49	0.818
	50–59	0.810
	>60	0.840

As mentioned in a previous section, a major limitation of these data was that the waiting list includes pre-dialysis patients. The publication reported an additional model used to calculate a utility decrement for time on dialysis (predialysis, <1 year, 1–3y, >3y). From these regression coefficients, a utility decrement for dialysis patients was derived from the waiting list-only model (0.024), which was subtracted from the waiting-list utilities above to provide the utilities as utilised in the model. These utilities are shown in Figure 17, alongside the derived general population utility.

Figure 17 Utilities versus age derived from Li et al. (2017)[36]



These data show that from the age of 63 years and above, the transplant patient utility is higher than that of the general population. The same is true for dialysis patients from the age of 82 years. This is clearly a counter-factual proposition, and so provides further justification for the use of Liem et al. (2008) in the base case.[35] This was corrected for in the scenario analysis by using the lower value of the general population or the derived utility in the model; thus, the utility cannot exceed that of the general population.

B.3.4.6 Caregiver disutility

Caregiver disutility is likely to be an important factor for dialysis patients. In particular, for those receiving HD, which is associated with an average of three treatments per week (can be up to seven days per week, depending on the type and schedule of dialysis). When this is also combined with the travel requirements to and from a dialysis centre, this can exert a large burden on carers. However, as the systematic literature review had failed to identify any relevant literature sources an additional targeted search on PubMed was conducted. This search aimed to identify the utility values/decrements for caregivers of patients undergoing dialysis. The scope of the targeted search was broad to identify literature impacts on caregiver HRQoL. Key search terms included “dialysis”, “caregiver”, “utility” and “quality of life”. Among the studies identified as assessing caregiver HRQoL in dialysis, very few used the EQ -5D. All studies identified consistently indicated an impact of the caregiver role on HRQoL, with a demonstration of poorer caregiver HRQoL compared with the general population.[84,85,86] This finding supported the inclusion of a caregiver utility decrement in the economic model. Three studies were identified that used the EQ-5D to assess caregiver HRQoL and, hence, provided applicable data for this economic model, these were: Thaweethamcharoen et al. (2020),[84] Gray et al. (2019),[85] and Nagawasa et al. (2018).[86] Of these, the study by Thaweethamcharoen et al. did not provide relative population norms within the paper, nor could published Thai estimates be located (from where the study derived), and so relative utility decrements could not be estimated from this study.[84]

Nagawasa et al. (2018) reported a caregiver utility of 0.873 in a study conducted in Japan on a population constituted of 25.5% males with an average age of 64.5 years old.[85] Gray et al. (2019) was conducted in China on a population with 40% males

and an average of 53.4 years old, and gave a caregiver utility of 0.869.[86] As the population norms are quite different in these two Asian countries compared to the UK, the utilities were first converted into UK utilities by multiplying them by a ratio of the UK population norm to the country (Japan or China) population norms. This led to estimated UK haemodialysis patient caregiver utilities of 0.803 and 0.783, respectively. These utilities were compared to the UK baseline population based on the relevant age and the proportion of males (using Equation 1 described in Section B.3.4.5.1). This led to caregiver utility decrements of 0.012 and 0.069 using the Japan and the China data, respectively. The utility decrement from the study by Nagawasa et al. was considered to be the more appropriate input source,[85] as Japan is a more comparable country to the UK and also as this was also the more conservative utility decrement. Alternative values for this assumption were applied in scenario analyses (using the alternative estimate of 0.069 or with no carer disutility).

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Details of the search strategies and the relevant evidence sources used for costs and healthcare resource data can be found in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Intervention

Imlifidase is administered as an infusion over 15 minutes, within 24 hours of the planned transplant. The model assumes that [redacted]% of patients will require a second infusion if negative crossmatch is not achieved (based on the proportion requiring a second dose within the clinical trial data). As the administration of imlifidase is a one-off event, this cost is considered only in the first cycle of the model. The proposed list price of imlifidase is £135,000 per vial, and a Patient Access Scheme has been submitted by Hansa Biopharma AB to PASLU that consists of a simple discount on the list price. This is a [redacted]% discount on the list price, meaning that imlifidase is available at a cost to the NHS of £[redacted] per vial and this cost is used in the base case of the model.

The model base case considers a weight-based dose administration and related costs for imlifidase. One vial of imlifidase is required for patients weighing ≤44kg, two vials for those weighing between 44–88kg, and three vials for patients who weigh ≥88kg. The proportion of patients requiring each number of vials is based on the baseline weights of the combined patient populations from all key imlifidase trials (13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06).

Table 43 summarises the costs of imlifidase treatment and concomitant medication (phenoxymethylpenicillin 1g/day). 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. No additional tests were considered for the administration of imlifidase as required crossmatch tests would already be considered part of the standard of care before a transplant. Although the SmPC for imlifidase does not require any concomitant medications with imlifidase, the utilisation of a prophylactic antibiotics (phenoxymethylpenicillin, 1g, once daily) for a duration of 14 days was added based a recommendation from a clinical expert in the UK. Similar use of prophylactic antibiotics occurred during the clinical trials of imlifidase.

Table 43 Cost of imlifidase and related co-medication

	Proportion	Cost (£)	Reference
Patients requiring 1 vial (≤44kg)	[redacted]	[redacted]	Section B.2.3.2
Patients requiring 2 vials (44–88kg)	[redacted]	[redacted]	Section B.2.3.2
Patients requiring 3 vials (≥88kg)	[redacted]	[redacted]	Section B.2.3.2
Average patient cost of imlifidase	[redacted]	[redacted]	
Average patient cost of imlifidase including those requiring second dose	[redacted]	[redacted]	Section B.2.6
Cost of co-medication (phenoxymethylpenicillin 1 g/day; OD)	100%	20.16	eMIT 2018[87]
Total average patient cost of treatment with imlifidase		[redacted]	—

OD: once daily

B.3.5.1.2 Comparator

As the comparator for this appraisal is dialysis, there is no direct comparator drug cost, with all costs being considered to be related to the dialysis health state. Therefore, the costs of dialysis are outlined in the health state costs section.

B.3.5.2 Health state costs

B.3.5.2.1 Transplant

The transplant procedure cost was taken from the NHS Reference Costs 2017-18.[88] In agreement with the patient population considered in this appraisal, only the costs corresponding to the cadaver, non-heart-beating donor and the cadaver, heart-beating donor for patients 19 years and over were used (codes LA01A and LA02A respectively). A weighted average based on the number of dialysis events was used. Pre-assessment and post-assessment visits (one each) were considered in addition to the procedure costs (codes LA12A and LA13A). Post-transplant care includes an intensive follow-up based on the Renal Association Clinical Practice guideline in post-operative care in the kidney transplant recipient.[89] Table 44 summarises the guidelines by month along with the derived number of nephrologist visits in the model based on the time since transplant. The cost of a nephrologist visit included the cost of integrated blood services.

Table 44 Number of post-transplant maintenance visits as derived from Renal Association Guidelines[89]

Period	Renal Association Guidelines	Derived number of nephrologist visits
Month 1	2–3 times weekly for the first month after transplantation	11
Months 2–3	1–2 times weekly for months 2–3	14
Months 4–6	Every 2–4 weeks for months 4–6	4
Total months 0–6 (model cycle 1)	Sum of above months	29
Total months 7–12 (model cycle 2)	Every 4–6 weeks	5
Subsequent years (model cycle 3+)	3–6 monthly	1.5 (3 per year)

Basiliximab was assumed to be used as induction therapy prior to undergoing transplant, in line with the recommendations of NICE TA481.[46] While basiliximab is

typically administered the day of the transplant and four days after, due to the mechanism of action of imlifidase, the use of basiliximab should be restricted to the fourth day when used in conjunction with imlifidase. The cost of basiliximab was taken from the British National Formulary (BNF).[90] Although basiliximab is administered by injection or infusion, no additional administration costs were accounted for as the patient would still be in hospital on day 4 post-transplant, and therefore, the administration cost of any drugs during the hospital stay would be accounted for in the transplant HRG code. A combination of tacrolimus, corticosteroids, and mycophenolate mofetil was considered as maintenance immunosuppressive therapy. Details on these therapies and the combined costs of transplant (including the procedure and maintenance therapy) are included in Table 45.

Table 45 Transplant costs used within model

Items		Unit cost	Number of units used	Total cost	Base case cost input (with inflation)	Reference
Transplant procedure cost	Physician pre-assessment	£408	1	£408	£418	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: LA12A)[88]
	Induction therapy	£842	1	£842	£862	One dose at 20 mg on Day 4 was considered based on restrictions associated with imlifidase. Cost: BNF[90]
	Transplant acute episode	£12,779	1	£12,779	£13,075	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: LA01A, LA02A)[88]
	Post-transplant assessment	£275	1	£275	£282	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: LA13A)[88]
	Total cost (cycle 1)				**£14,636**	SE: 1,464; 95% CI: 11,768–17,505
Transplant maintenance cost (0–6 months)	Follow-up visits	£181	29	£5,241	£5,362	Usage derived in Table 44 based on Renal Association Guidelines;[89] Cost: National Schedule of Reference Costs - Year 2017–18 - Outpatient Attendances Data (Service code: 361) & Blood test (Code: DAPS03)[88]
	Tacrolimus	£7.63	183	£1,394	£1,394	Dosage: 0.1mg/kg/day at day 1, 5.01mg/day at day 365 (Budde 2014);[91] Cost: Drug Tariff December 2019 (Adoport 2mg)[92]
	Corticosteroids	£0.01	183	£2	£2	Dosage: 5 mg daily (Baker 2017);[89] Cost: eMIT 2018 (Prednisolone 5mg tablets / Packsize 28)[87]
	Mycophenolate	£0.68	183	£124	£124	Dosage: 1g twice daily (Mycophenolate mofetil SmPC);[93] Cost:eMIT 2018

	mofetil					(Mycophenolate mofetil 500mg tablets / Packsize 50)[87]
	Total cost (cycle 1)				**£6,882**	SE: 688; 95% CI: 5,533–8,231
Transplant maintenance cost (7–12 months)	Follow-up visits	£181	5	£904	£925	Usage derived in Table 44 based on Renal Association Guidelines;[89] Cost: National Schedule of Reference Costs - Year 2017–18 - Outpatient Attendances Data (Service code: 361) & Blood test (Code: DAPS03)[88]
	Tacrolimus	£6.25	183	£1,142	£1,142	Dosage: 0.1mg/kg/day at day 1, 5.01mg/day at day 365 (Budde 2014);[91] Cost: Drug Tariff December 2019 (Adoport 2mg)[92]
	Corticosteroids	£0.01	183	£2	£2	Dosage: 5 mg daily (Baker 2017);[89] Cost: eMIT 2018 (Prednisolone 5mg tablets / Packsize 28)[87]
	Mycophenolate mofetil	£0.68	183	£124	£124	Dosage: 1g twice daily (Mycophenolate mofetil SmPC);[93] Cost:eMIT 2018 (Mycophenolate mofetil 500mg tablets / Packsize 50)[87]
	Total cost (cycle 2)				**£2,192**	SE: 219; 95% CI: 1,762–2,621
Transplant maintenance cost (after Year 1)	Follow-up visits	£181	1.5	£272	£278	Usage derived in Table 44 based on Renal Association Guidelines;[89] Cost: National Schedule of Reference Costs - Year 2017–18 - Outpatient Attendances Data (Service code: 361) & Blood test (Code: DAPS03)[88]
	Tacrolimus	£5.56	183	£1,016	£1,016	Dosage: 0.1mg/kg/day at day 1, 5.01mg/day at day 365 (Budde 2014);[91] Cost: Drug Tariff December 2019 (Adoport 2mg)[92]
	Corticosteroids	£0.01	183	£2	£2	Dosage: 5 mg daily (Baker 2017);[89] Cost: eMIT 2018 (Prednisolone 5mg tablets /

						Packsize 28)[87]
	Mycophenolate mofetil	£0.68	183	£124	£124	Dosage: 1g twice daily (Mycophenolate mofetil SmPC);[93] Cost: eMIT 2018 (Mycophenolate mofetil 500mg tablets / Packsize 50)[87]
	Total cost (cycle 3+)				**£1,418**	SE: 142; 95% CI: 1,140–1,696

CI: confidence interval; SE: standard error

B.3.5.2.2 Dialysis

The cost of dialysis and its derivation is summarised in Table 47. The cost of haemodialysis (hospital, satellite clinic, and home dialysis) and peritoneal dialysis were derived from the UKRR Annual Report and NHS Reference Costs 2017–18 using the codes for patients aged 19 years and over, to reflect the adult population under consideration by this model.[9,88] A weighted average cost was calculated using the proportion of dialysis patients recorded within the UKRR Annual Report.[9] An annual total of four nephrologist visits were considered based on guidance based on UK clinical expert opinion. The costs of a nephrologist visit were assumed to also include the cost of integrated blood services, and were based on the NHS Reference Costs 2017–18.[88]

No initial dialysis access procedure costs were considered because the population for this model includes patients that are already on RRT. It is assumed that highly sensitised patients that are unlikely to be transplanted would already be on dialysis at the time they receive the kidney transplant (no pre-emptive transplant are expected for this population), and, therefore, dialysis access would already be in place. In addition, dialysis access needs to mature before patients start treatment. As such, dialysis access procedures are performed preventively. The duration of a fistula is, however, not unlimited and re-access procedures may become necessary. According to the dialysis clinical expert consulted, there is a lot of variation in the duration of a fistula from one patient to another. The duration depends mainly on the age of the patient and any comorbidities. The clinical expert estimated that an average duration, for a patient 45 years old was 6–7 years, whilst this would be closer to 3–4 years for a patient 65 years old. These average durations could be shortened for a patient with comorbidities, such as severe diabetes. However, given that the patients in the economic model are sufficiently healthy to be on the transplant list, these optimistic assumptions are assumed to be the most relevant. For simplicity, a conservative duration of 6 years for a fistula was used in the model regardless of age. This was converted into a per cycle probability, which resulted in approximately 0.11 access procedures performed annually per patient as a cost for HD.

The utilisation of conventional erythropoiesis-stimulating agents (ESA) was considered for dialysis patients. The proportion of ESA utilisation and the weekly dosage for HD and PD patients was based on information reported in the UKRR Annual Report,[80] whilst the costs were based on the NHS Drug Tariff 2019, using a conservative cost of epoetin zeta (minimum reported).[92]

As transport costs are reimbursed by NHS for patients on dialysis, these costs were applied for the hospital and satellite haemodialysis patients. Table 46 summarises the transport costs considered within the model. The usage of different modalities of transport were taken from the National Kidney Care Audit, Patient Transport Survey 2010.[94] The cost of an ambulance was taken from the NHS treatment and ambulance journey charges for 2019;[95] while the cost for the other type of transports were taken from Liu et al. (2015),[96] adjusted to 2019 British pounds. The annual cost was calculated for each dialysis type (HD and PD) and a weighted average was calculated based on the prevalent number of patients on HD and on PD in England according to the UKRR 21st Annual Report.[80] This is converted to produce the per cycle (6-month) dialysis cost utilised by the model.

Table 46 Dialysis transport costs

Type of transport	Percentage utilisation (based on patient transport survey 2010)[94]	Unit cost	Adjusted average cost (including inflation & utilisation)	Reference
Ambulance service vehicle	18%	£219	£39	NHS treatment and ambulance journey charges for 2019[95]
Hospital-provided car	12%	£27	£3	Liu et al. (2015)[96]
Hospital-arranged taxi	12%	£31	£4	Liu et al. (2015)[96]
Hospital transport vehicle	22%	£13	£3	Liu et al. (2015)[96]
By their own means	36%	£0	£0	
Average patient cost			**£50**	

Table 47 Dialysis costs used within model

Items		Unit cost	Number of units used	Total annual cost	Weight	Adjusted total annual cost input (with weight & inflation)	Reference
Haemodialysis	Hospital haemodialysis	£158	156	£24,634	37%	£9,355	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: LD01A, LD02A, LD03A, LD04A)[88]
	Satellite haemodialysis	£145	156	£22,632	59%	£13,606	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: LD05A, LD06A, LD07A, LD08A)[88]
	Home haemodialysis	£230	156	£35,895	4%	£1,516	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: LD09A, LD10A)[88]
	Haemodialysis access	£2,294	0.11	£250	100%	£256	Usage based on clinical expert opinion that average duration of haemodialysis fistula is 6 years; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: YQ42Z)[88]
	Nephrologist visits	£181	4	£723	100%	£740	Usage based on Renal Association Guidelines;[89] Cost: National Schedule of Reference Costs - Year 2017–18 - Outpatient Attendances Data (Service code: 361) + Blood test (Code: DAPS03)[88]
	Haemodialysis ESA cost	£4.81	416	£2,000	92.6%	£1,852	Usage based on UK Renal Registry 20th Annual Report

							(Chapter 7 Haemoglobin, Ferritin and Erythropoietin in UK Adult Dialysis Patients in 2016, median dose);[97] Cost: NHS Drug Tariff 2019 (Minimum cost of epoetin zeta)[92]
	Transport cost per visit	£50	156	£7,784	96%	£7,463	See Table 46 for derivation; Applied to hospital and satellite dialysis only
	Total cost					**£34,787**	
Peritoneal dialysis	Peritoneal dialysis	£74	365	£27,209	100%	£27,839	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: LD11A, LD12A, LD13A)[88]
	Nephrologist visits	£181	4	£723	100%	£740	Usage based on Renal Association Guidelines;[89] Cost: National Schedule of Reference Costs - Year 2017–18 - Outpatient Attendances Data (Service code: 361) + Blood test (Code: DAPS03)[88]
	Haemodialysis ESA cost	£4.81	208	£1,000	78.6%	£786	Usage based on UK Renal Registry 20th Annual Report (Chapter 7 Haemoglobin, Ferritin and Erythropoietin in UK Adult Dialysis Patients in 2016, median dose);[97] Cost: NHS Drug Tariff 2019 (Minimum cost of epoetin zeta)[92]
	Total cost					**£29,365**	
Total dialysis cost	Haemodialysis			£34,787	78%	£27,205	Weighting based on UK Renal Registry Annual Report;[9] Costs:

							derived above
	Peritoneal dialysis			£29,365	22%	£6,400	Weighting based on UK Renal Registry Annual Report;[9] Costs: derived above
	Total annual cost					£33,605	
	Total cost per cycle					**£16,803**	SE: 1,680; 95% CI: 13,509–20,096

CI: confidence interval; ESA: erythropoiesis-stimulating agents; SE: standard error

B.3.5.3 Adverse reaction unit costs and resource use

B.3.5.3.1 Imlifidase-related adverse events

AEs related to imlifidase and kidney transplant were included in the model (as detailed in Section B.3.4.4). Table 48 summarises the costs applied to the AEs experienced within the model, and the rates of incidence of these AEs are reported in Table 37.

Table 48 Imlifidase-related adverse event costs

AEs	Cost per episode	SE (£)	95% CI (£)	Reference
Pneumonia	£1,825	183	1,467–2,183	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: DZ11K, DZ11L, DZ11M, DZ11N, DZ11P, DZ11Q, DZ11R, DZ11S, DZ11T, DZ11U, DZ11V)[88]; Weighted average of costs inflated to 2019 prices
Sepsis	£2,217	222	1,782–2,651	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: WJ06A, WJ06B, WJ06C, WJ06D, WJ06E, WJ06F, WJ06G, WJ06H, WJ06J)[88]; Weighted average of costs inflated to 2019 prices
Abdominal infection	£3,565	356	2,866–4,263	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: HE81A, HE81B, HE81C)[88]; Weighted average of costs inflated to 2019 prices
Catheter site infection	£1,871	187	1,505–2,238	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: WH07A, WH07B, WH07C, WH07D, WH07E, WH07F, WH07G)[88]; Weighted average of costs inflated to 2019 prices
Parvovirus infection	£1,326	133	1,066–1,586	Assumes one treatment with IVIg. National Schedule of Reference Costs - Year 2017–18 - High Drug Cost (Normal immunoglobulin, Admitted patient care)[88]
Upper respiratory tract infection	£665	66	535–795	National Schedule of Reference Costs - Year 2017–18 - HRG Data (Codes: DZ19H, DZ19J, DZ19K, DZ19L, DZ19M, DZ19N)[88]; Weighted average of costs inflated to 2019 prices
Infusion-related reaction	£0	0	0–0	In trial15-HMedIdeS-06, infusion-related reactions were determined to be allergies and were treated with an antihistaminic (dexchlorpheniramine), which costs in Europe €5.40 for 20 tablets; Cost was

				therefore set to £0 in model
Myalgia	£0	0	0–0	Assumption made that muscle relaxants would be used to treat myalgia. Baclofen costs £1.58–9.99 for 84 tablets in UK; Cost was therefore set to £0 in model

CI: confidence interval; IVIg, intravenous immunoglobulin; SE: standard error

B.3.5.3.2 Transplant-related adverse events

The costs associated with the treatment of transplant-related adverse events are summarised in Table 49, and includes AMR, delayed graft function, and graft loss. The treatment for AMR was discussed with UK clinical experts who reported that the standard of care includes: intravenous methylprednisolone for three days; plasma exchange; IVIg; adjustment of tacrolimus dosage and adjustment of the mycophenolate mofetil. The cost of plasma exchange was based on the NHS Reference Costs 2017–18 using the HRG data (code SA14Z);[88] this already includes the costs of inpatient stay and associated resources (including low-cost drugs administered in hospital). For this reason, the cost of intravenous methylprednisolone was not included. As the patients are highly sensitised, it was already assumed, in the maintenance immunosuppressant costing that the maximum dosage for mycophenolate mofetil would be used (2g per day), so no increase in dosage was considered in case of an AMR. As tacrolimus dosing needs to be continually adapted based on trough levels, there are no standard dosage recommendations, and an average dosage was used in the maintenance immunosuppressant costing that already included adjustment based on the tacrolimus level. For this reason, the tacrolimus adjustments were also not considered in the costing of AMR. According to the clinical experts in the UK, treatments with rituximab, anti-thymocyte globulin, and more rarely in the UK, bortezomib could also be used. The utilisation proportions of these treatments are based on their clinical expert opinion.

For delayed graft function, an average duration of 20 days was considered. During this period, it was assumed, based on discussions with UK clinical experts that the patient would remain on dialysis, and that there would be a once-weekly biopsy and ultrasound scan performed, for a total of 3 of each during the 20-day period.

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 was taken from data utilised during previous NICE appraisals (used in TA481, and originally derived for TA165 based on NHSBT data).[46,98] As the cost-effectiveness model for imlifidase presented here uses a 6-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 (32%), 23% was used for the second cycle, 9% for the third and fourth cycles, and 4% on the remaining cycles of the model.[98] The cost of nephrectomy was based on the NHS Reference Costs 2017–18.[88] In addition to the cost of nephrectomy, the model assumed that if the graft loss occurs within the first 6 months, immunosuppressive therapy would be stopped whilst steroids are maintained for 3 months. If the graft is lost after 6 months, immunosuppressive therapy would continue for an additional month, while steroids are maintained for three months. Finally, it was assumed that the dialysis access would not have been closed for most patients receiving a transplant and this was still usable for most patients in the case of a return to dialysis. It was, however, assumed that 10% of patients would need a re-access to be performed. This pathway of care is based on a discussion with UK clinical experts and was expressed to be considered standard practice in England.

Table 49 Transplant-related adverse event costs

		Unit cost	Number of units used	Percentage utilisation	Cost per episode (with utilisation)	Adjusted cost per episode (with utilisation & inflation)	Reference
AMR (Cycle 1)	Plasma exchange	£7,628	1	100%	£7,628	£7,805	National Schedule of Reference Costs - Year 2017–18 - HRG data (Code: SA14Z)[88]
	IVIg	£1,296	1	100%	£1,296	£1,326	National Schedule of Reference Costs - Year 2017–18 - High Drug Cost (Normal immunoglobulin, Admitted patient care)[88]
	Rituximab	£1,234	1	50%	£617	£631	National Schedule of Reference Costs - Year 2017–18 - High Drug Cost (Rituximab, Admitted patient care)[88]
	Bortezomib	£1,005	1	10%	£101	£103	National Schedule of Reference Costs - Year 2017–18 - High Drug Cost (Bortezomib, Admitted patient care)[88]
	ATG	£3,832	1	30%	£1,149	£1,176	National Schedule of Reference Costs - Year 2017–18 - High Drug Cost (Antithymocyte Immunoglobulin, Admitted patient care)[88]
	Total cost					**£11,041**	SE: 1,104; 95% CI: 8,877–13,205
Delayed graft function (Cycle 1)	Dialysis	£92	20	100%	£1,840	£1,840	Assumption that dialysis is required for 20 days; Cost based on 20 days of dialysis using cost detail in Table 47
	Biopsy	£783	3	100%	£2,350	£2,405	Assumption that weekly biopsy required; National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: YL20A)[88]

	Ultrasound scans	£54	3	100%	£161	£165	Assumption that weekly ultrasound scans required; National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: RD40Z)[88]
	Total cost					**£4,409**	SE: 441; 95% CI: 3,545–5,274
Graft Loss (Cycle 1)	Nephrectomy	£6,391	1	32%	£2,045	£2,093	Rate of nephrectomy based on NICE TA165;[98] National Schedule of Reference Costs - Year 2017–18 - HRG data (Codes: LB60C, LB60D, LB60E, LB60F, LB61C, LB61D, LB61E, LB61F, LB61G, LB62C, LB62D, LB63C, LB63D)[88]
	Insertion of tunnelled CVC	£924	1	10%	£92	£95	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG data (Code: YR41A)[88]
	Access surgery	£1,978	1	10%	£198	£202	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: YQ42Z,LA05Z);[88] these costs are weighted by proportion of HD/PD based on UK Renal Registry Annual Report[9]
	Maintenance immunosuppression	£1.01	1	100%	£1	£1	Assumption that if graft loss occurs within the first 6 months, immunosuppressants are stopped but steroids would be maintained for 3 months (cost as in Table 45)
	Total cost					**£2,391**	SE: 239; 95% CI: 1,922–2,859
Graft Loss (Cycle 2)	Nephrectomy	£6,391	1	23%	£1,470	£1,504	Rate of nephrectomy based on NICE TA165;[98] National Schedule of Reference Costs - Year 2017–18 - HRG data (Codes: LB60C, LB60D, LB60E, LB60F,

							LB61C, LB61D, LB61E, LB61F, LB61G, LB62C, LB62D, LB63C, LB63D)[88]
	Insertion of tunnelled CVC	£924	1	10%	£92	£95	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG data (Code: YR41A)[88]
	Access surgery	£1,978	1	10%	£198	£202	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: YQ42Z,LA05Z);[88] these costs are weighted by proportion of HD/PD based on UK Renal Registry Annual Report[9]
	Maintenance immunosuppression	£181	1	100%	£181	£191	Assumption that if the graft loss occurs after the first 6 months, immunosuppressants (tacrolimus and mycophenolate mofetil) are used for 1 month and steroids maintained for 3 months (cost as in Table 45)
	Total cost					**£1,992**	SE: 199; 95% CI: 1,601–2,382
Graft Loss (Cycle 3)	Nephrectomy	£6,391	1	9%	£575	£589	Rate of nephrectomy based on NICE TA165;[98] National Schedule of Reference Costs - Year 2017–18 - HRG data (Codes: LB60C, LB60D, LB60E, LB60F, LB61C, LB61D, LB61E, LB61F, LB61G, LB62C, LB62D, LB63C, LB63D)[88]
	Insertion of tunnelled CVC	£924	1	10%	£92	£95	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG data (Code: YR41A)[88]
	Access surgery	£1,978	1	10%	£198	£202	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of

							Reference Costs - Year 2017–18 - HRG Data (Code: YQ42Z,LA05Z);[88] these costs are weighted by proportion of HD/PD based on UK Renal Registry Annual Report[9]
	Maintenance immunosuppression	£181	1	100%	£181	£191	Assumption that if the graft loss occurs after the first 6 months, immunosuppressants (tacrolimus and mycophenolate mofetil) are used for 1 month and steroids maintained for 3 months (cost as in Table 45)
	Total cost					**£1,076**	SE: 108; 95% CI: 865–1,287
Graft Loss (Cycle 4)	Nephrectomy	£6,391	1	9%	£575	£589	Rate of nephrectomy based on NICE TA165;[98] National Schedule of Reference Costs - Year 2017–18 - HRG data (Codes: LB60C, LB60D, LB60E, LB60F, LB61C, LB61D, LB61E, LB61F, LB61G, LB62C, LB62D, LB63C, LB63D)[88]
	Insertion of tunnelled CVC	£924	1	10%	£92	£95	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG data (Code: YR41A)[88]
	Access surgery	£1,978	1	10%	£198	£202	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: YQ42Z,LA05Z);[88] these costs are weighted by proportion of HD/PD based on UK Renal Registry Annual Report[9]
	Maintenance immunosuppression	£181	1	100%	£181	£191	Assumption that if the graft loss occurs after the first 6 months, immunosuppressants (tacrolimus and

							mycophenolate mofetil) are used for 1 month and steroids maintained for 3 months (cost as in Table 45)
	Total cost					**£1,076**	SE: 108; 95% CI: 865–1,287
Graft Loss (Cycle 5+)	Nephrectomy	4%	£6,391	1	£256	£262	Rate of nephrectomy based on NICE TA165;[98] National Schedule of Reference Costs - Year 2017–18 - HRG data (Codes: LB60C, LB60D, LB60E, LB60F, LB61C, LB61D, LB61E, LB61F, LB61G, LB62C, LB62D, LB63C, LB63D)[88]
	Insertion of tunnelled CVC	£924	1	10%	£92	£95	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG data (Code: YR41A)[88]
	Access surgery	£1,978	1	10%	£198	£202	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: YQ42Z, LA05Z);[88] these costs are weighted by proportion of HD/PD based on UK Renal Registry Annual Report[9]
	Maintenance immunosuppression	£181	1	100%	£181	£191	Assumption that if the graft loss occurs after the first 6 months, immunosuppressants (tacrolimus and mycophenolate mofetil) are used for 1 month and steroids maintained for 3 months (cost as in Table 45)
	Total cost					**£749**	SE: 75; 95% CI: 603–896

AMR: antibody mediated rejection; ATG: anti-thymocyte globulin; CVC: central venous catheter; HD: haemodialysis; IVIg: intravenous immunoglobulin; PD: peritoneal dialysis

B.3.5.3.3 Dialysis-related adverse events

The costs used for dialysis-related AEs are summarised in Table 50 (for costs associated with HD) and Table 51 (for costs associated with peritonitis). It was assumed that all patients suffering from peritonitis would require antibiotics for 3 weeks. In addition, clinical expert opinion advised that 8–9% of peritonitis episodes for patients on the transplant list would require surgery. The model assumed that 8% of the peritonitis patients will require surgery to insert a central venous catheter and to remove the peritoneal access. As the central venous catheter is a temporary solution, the cost of new access surgery was also added. Costs for these procedures were derived from the relevant HRG codes within the National Schedule of Reference Costs (details in Table 51).[88] The proportion of patients that would have an access created for HD or PD was assumed to be the same as the proportion of patients on each of these modalities within the model (78% HD and 22% PD, taken from UKRR Annual Report).[9] This aligns well with the clinical expert opinion that for one in four patients with peritonitis leading to surgery and the installation of a central venous catheter, a new peritoneal dialysis access will be created, while the other three out of four would remain on haemodialysis permanently. For the cost of a chest infection, the HRG codes for “Unspecified acute lower respiratory infection” were used (DZ22K, DZ22L, DZ22M, DZ22N, DZ22P, DZ22Q) and averaged based on the number of activities.[88] For Stenosis the HRG code YR48Z for “Attention to arteriovenous fistula, graft or shunt” was used.[88] Whilst this does not provide a comprehensive analysis of all AEs related to dialysis, it does include the most significant that are likely to have the largest impact on this analysis (as confirmed by UK clinical expert opinion). This approach is likely to be conservative in respect to the cost-effectiveness of imlifidase, as additional adverse events that are not included here are likely to incur some additional costs for dialysis.

Table 50 Costs of dialysis adverse events

Type of cost	Cost per episode	SE	95% CI	Reference
Chest infection (HD patients)	£1,121	112	901–1,341	National Schedule of Reference Costs - Year 2017–18 (Codes: DZ22K, DZ22L, DZ22M, DZ22N, DZ22P, DZ22Q)[88]
Stenosis (HD patients)	£1,307	131	1,051–1,563	National Schedule of Reference Costs - Year 2017–18 (Code: YR48Z)[88]

CI: confidence interval; HD: haemodialysis; SE: standard error

Table 51 Peritonitis costs

	Unit cost	Number of units used	Percentage utilisation	Cost per episode (with utilisation)	Adjusted cost per episode (with utilisation & inflation)	Reference
Antibiotics	£1.01	21	100%	£21	£21	Proportion of utilisation: Clinical expert opinion; Cost: eMIT 2018[87]
Removal of the PD catheter	£845	1	8%	£68	£69	Proportion of utilisation: Clinical expert opinion; Cost: National Schedule of Reference Costs - Year 2017–18 - HRG data (Code: LA05Z)[88]
Insertion of tunnelled CVC	£924	1	8%	£74	£76	Proportion of utilisation: Clinical expert opinion; Cost: National Schedule of Reference Costs - Year 2017–18 - HRG data (Code: YR41A)[88]
Access surgery	£1,978	1	8%	£158	£162	Proportion of utilisation: Clinical expert opinion; Costs: National Schedule of Reference Costs - Year 2017–18 - HRG Data (Code: YQ42Z, LA05Z);[88] these costs are weighted by proportion of HD/PD based on UK Renal Registry Annual Report[9]
Total cost					**£328**	SE: 33; 95% CI: 264–392

CI: confidence interval; CVC: central venous catheter; PD: peritoneal dialysis; SE: standard error

B.3.5.4 Miscellaneous unit costs and resource use

There are no other miscellaneous costs within this economic model.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

The base case inputs for the economic model are summarised in Table 52.

Table 52 Summary of variables applied in the economic model base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Time horizon	Lifetime (57 years)	NA (NA)	Section B.3.2.2
Discount rate (outcomes and costs)	3.5%	NA (NA)	Section B.3.2.2
Age at baseline	45 (Table 29)	36–54 (gamma distribution)	Section B.3.3.1
Proportion female	60% (Table 29)	48–71 (beta distribution)	Section B.3.3.1
Graft survival	iBox data (Figure 9)	NA (normal distribution)	Section B.3.3.2.1
Patient survival	All imlifidase data (Figure 13)	NA (normal distribution)	Section B.3.3.3.1
Dialysis survival	UKRR data (Table 36)	NA (normal distribution)	Section B.3.3.4
Baseline utilities	Age and gender dependent utilities (Equation 1)	NA (NA)	Section B.3.4.5.1
Carer disutility	0.012 (Section B.3.4.6)	NA (NA)	Section B.3.4.6
HD disutility	0.276 (Table 41)	0.216–0.346 (gamma distribution)	Section B.3.4.5.2
PD disutility	0.263 (Table 41)	0.173–0.343 (gamma distribution)	Section B.3.4.5.2
Functioning graft disutility	0.053 (Table 41)	-0.037–0.143 (gamma distribution)	Section B.3.4.5.2
Imlifidase acquisition cost	£[redacted] per vial (Table 43)	NA (NA)	Section B.3.5.1.1
Proportion of patients requiring 1/2/3 vials	[redacted] (Table 43)	[redacted] (Dirichlet distribution)	Section B.3.5.1.1
Proportion of patients requiring second dose	[redacted] (Table 43)	[redacted]	Section B.3.5.1.1

Co-medication cost	£20.16 (Table 43)	£16.21–£24.11	Section B.3.5.1.1
Transplant health state costs	Table 45	Table 45 (gamma distribution)	Section B.3.5.2.1
Dialysis health state costs	Table 47	Table 47 (gamma distribution)	Section B.3.5.2.2
Proportion using HD	78.2% (Table 47)	62.9–93.5%	Section B.3.5.2.2
Imlifidase related AEs incidence	Table 37	Table 37 (beta distribution)	Section B.3.4.4.1
Imlifidase related AEs costs	Table 48	Table 48 (gamma distribution)	Section B.3.5.3.1
Transplant related AEs incidence	Table 38	Table 38 (beta distribution)	Section B.3.4.4.2
Transplant related AEs costs	Table 49	Table 49 (gamma distribution)	Section B.3.5.3.2
Dialysis AEs incidence	Table 39	Table 39 (beta distribution)	Section B.3.4.4.3
Dialysis AEs costs	Table 50 and Table 51	Table 50 and Table 51 (gamma distribution)	Section B.3.5.3.3

AE: adverse event; CI: confidence interval; HD: haemodialysis; NA: not applicable; PD: peritoneal dialysis; UKRR: United Kingdom Renal Registry

B.3.6.2 Assumptions

The key assumptions made for this model are summarised in Table 53.

Table 53 Key assumptions in economic model

Assumption	Justification
Lifetime horizon	This model focusses on patients who have a chronic condition that they will have for the rest of their lives. Therefore, it is reasonable to conclude that a lifetime horizon is most suitable in this situation, and this is consistent with the NICE reference case.
Model cycle length of 6 months	The choice of the cycle duration was based on the consideration that clinically meaningful events typically happen in this disease within 6 months of treatment. For example, clinical events such as AMR typically happen in the first 6 months following transplant. Due to the length of the cycles, a half-cycle correction was applied to the model.
Dialysis is the relevant comparator	The licensed indication for imlifidase includes only highly sensitised patients with a positive crossmatch to a deceased donor transplant and unlikely to receive a transplant through any appropriate allocation schemes. The target population of this model, therefore, only includes patients who are unable to receive a transplant without treatment with imlifidase. Therefore, in the absence of imlifidase, the only available treatment option available to these patients is dialysis, and, hence, this is the relevant comparator for this economic model.
Imlifidase patients enter the model into	All patients successfully transitioned from having a positive to a negative crossmatch and received a transplant. This is based on the

the functioning graft health state of the model	results from the imlifidase trials (see Section B.2.8.2.2), where all patients achieved crossmatch conversion and received a kidney transplant.
No treatment waning is considered in the model	Imlifidase is administered as a single treatment before transplant and so there is no long-term treatment where treatment waning would be considered appropriate.
Long-term rates of graft loss following imlifidase	Due to the innovative nature of imlifidase, currently there is a lack of long-term efficacy data on this treatment. Therefore, assumptions have had to be made on how to best model the long-term efficacy of this treatment. For graft loss, the validated iBox tool (which has been validated in patients relevant to this analysis) was utilised to produce a prediction of graft loss over 10 years based on the available patient data for imlifidase.[79] This was then extrapolated over the lifetime of the model using statistical techniques, with the most appropriate technique judged by the goodness of fit to the iBox data.
Mortality from functioning graft health state	Due to the innovative nature of imlifidase, there is currently a lack of long-term efficacy data on this treatment. Therefore, assumptions have had to be made on how to best model the long-term efficacy of this treatment. For mortality, this was modelled based on the available data on imlifidase. This was then extrapolated over the lifetime of the model using statistical techniques, with the most appropriate technique judged by the goodness of fit to the available data.
Mortality from dialysis health state	Dialysis was assumed to lead to an excess mortality above background levels. This was modelled in a similar manner to that previously used in NICE TA481,[46] and utilises data from the UKRR to provide details on excess mortality in dialysis recipients.
Utilities in model are based on published data	No available data were available for imlifidase patients from the clinical trials. Additionally, as the trials contained no comparator there was no ability for the trials to provide data for both arms of the model. The most suitable published data were identified to populate the model. In addition, to account for potential differences in populations, the base case included a baseline utility calculated based on age and gender. This ensures that the most appropriate utilities available are utilised within this model.
Caregiver disutility not based on UK data	Empirical data on caregiver disutility in relation to ESRD within the UK are lacking. However, due to the burden placed on caregivers from dialysis due to travel requirements and treatment requirements (especially for home dialysis) this can be seen to be an important factor in the consideration of dialysis. The only available literature sources were from Asian countries and so their applicability to the UK is questionable. The lower value from these sources (0.012) was used as a conservative estimate; it was also considered more relevant as it used Japanese data (rather than Chinese data). Adjustments were made to the value to try and address differences between the countries, and this is the best available estimate given the very limited data in this area.
Dialysis AEs not fully included in model	Only limited dialysis AEs have been able to be included in the model based on a lack of data around the incidence and severity of these events. Discussions with clinical experts have highlighted that dialysis is associated with a number of AEs, particularly after long-

	term dialysis. This highlights that the model is unlikely to include the full impact and costs of dialysis (although clinical expert opinion has been used to include all of the most impactful dialysis AEs). Overall, this is likely to provide a conservative estimate for the ICER of imlifidase in comparison to dialysis.
ESRD related AEs not included in model	There is a lack of detailed published evidence of complications related to ESRD (such as cardiovascular events and infections). These AEs could, therefore, not be included within the economic model. It would be expected that these events would have minimal impact on the results of the economic analysis, as they would be experienced equally within both arms.
A number of resource use inputs are based on clinical expert opinion	In areas where no clear guidelines for treatment exist (for example, treatment of AMR and immunosuppressive therapy after graft loss), clinical expert opinion was utilised to ensure the model matches standard UK NHS treatment practice.
Post-graft failure treatment	It is assumed that following graft failure, patients would resume dialysis immediately with an added consideration of the costs associated with graft failure (nephrectomy and continued immunosuppressive therapy).
Weight of imlifidase patients based on clinical trial data	As imlifidase requires weight-based dosing, it is required to estimate the proportion of patients falling into each weight category. The most relevant and appropriate assumption was to use the data on patient weight from the imlifidase trials.
Not all dialysis costs are included within the model	Due to a lack of published data, not all dialysis costs have been able to be included within the model. This includes costs associated with dialysis-related AEs.
Re-transplants are not possible in the model	Imlifidase treatment may only be used for one transplant per patient and so re-transplants with the use of imlifidase are, thus, not possible. As the patients have to be classed as highly sensitised and unlikely to be transplanted to be eligible for imlifidase, it is assumed that they would be unable to receive a re-transplant through any other means.
Impact on work productivity not included in model	The negative impacts of health states (particularly dialysis) on work productivity have not been included within the model as they fall outside the NICE reference case. Similarly, the economic benefits of increased work productivity associated with transplant are not captured within this model.
Equality impacts not considered within the economic model	The potential equality impacts of imlifidase are beyond the scope of this economic analysis and relate mainly to access. Therefore, it was not possible for any equality impacts to be considered within the economic model.

AE: adverse event; AMR: antibody-mediated rejection; ESRD: end stage renal disease; ICER: incremental cost-effectiveness ratio; UKRR: United Kingdom Renal Registry

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

The base case results of the cost-effectiveness analysis for imlifidase are summarised in Table 54. Although the imlifidase patients incur higher total costs, over the lifetime horizon, there was a substantial gain in QALYs for patients who were treated with imlifidase compared with those who remained on dialysis ([redacted] vs [redacted], respectively), which led to an incremental cost-effectiveness ratio (ICER) of £30,641 per QALY. It is worthy of note that the QALY gain with imlifidase is composed of a substantial gain in life years ([redacted] for imlifidase vs [redacted] for dialysis) that is associated with the increased survival of patients following transplant. The ICER result was further analysed through sensitivity analyses addressing any source of uncertainty in the parameters and structure of the model, as detailed in the following section.

Table 54 Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Imlifidase and transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,641
Dialysis	[redacted]	[redacted]	[redacted]				

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year

Disaggregated costs and QALY information is presented in Appendix J. This demonstrates that the higher cost for imlifidase patients is primarily due to the cost of treatment. However, this cost is partially offset by the higher cost of dialysis over the functioning graft health state, throughout the time horizon. These disaggregated data also highlight that the QALY gain for imlifidase patients is based on their time within the functioning graft health state (since in the absence of imlifidase, dialysis patients do not have access to this health state).

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty of the parameters. The Monte Carlo simulation was run for 10,000 PSA iterations with parameters values drawn from probabilistic density functions. Details on the distributions used for each variable are included within Table 52.

B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analyses were conducted in order to explore the sensitivity of the parameters. For these, parameters were varied in isolation between the estimated lower and upper values (as detailed within Table 52) and model results were recorded. In cases where the CI of a parameter was unknown, an estimate was used assuming a standard error of 10% of the mean value. The impact of these input changes on the ICER was examined and results presented in a tornado diagram.

B.3.8.3 Scenario analysis

The following scenarios were considered in additional analyses.

B.3.8.3.1 Alternative discounting

The reference case 3.5% discount rate was varied from 0% to 6% in one of the one-way sensitivity analysis. An alternative discounting rule was assessed where a discount rate of 1.5% was considered in a scenario analysis.

B.3.8.3.2 Alternative time horizon

Although the lifetime time horizon in the base case analysis is the most relevant timeframe given the chronic nature of renal replacement therapy, an alternative time horizon of 20 years was applied in a scenario analysis in order to assess the impact of a shorter timeframe on the results.

B.3.8.3.3 Alternative source for the utilities

Whereas the base case used the general population utilities as baseline values that were adjusted with utility decrement based on Liem et al. (2008),[35] a sensitivity analysis using a UK specific study, Li et al. (2017),[36] was considered in a scenario

analysis. In this study, EQ-5D-5L utilities were regressed on patient baseline characteristics, including age and RRT status (transplant or waiting list). See Section B.3.4.5.3 for more information.

Two additional scenario analyses were conducted on caregiver utility decrements for the HD patients: one based on setting this decrement to zero; and one based on an alternative literature source. See Section B.3.4.6 for additional information.

B.3.8.3.4 Alternative sources for the graft survival

While the base case used the iBox predictions, two graft loss scenario analyses were performed using extrapolations of the death-censored graft loss based on the observed data from imlifidase trials:

- Using the all imlifidase data as described in Section B.3.3.2.2
- Using the 'unlikely to be transplanted' population as described in Section B.3.3.2.3

B.3.8.3.5 Alternative source for the patient survival with a functioning graft

The all imlifidase data is considered to be the most reliable dataset as it contains a much greater number of patients than the 'unlikely to be transplanted' group. The extrapolations of patient survival for the 'unlikely to be transplanted' population were also performed and presented in a scenario analysis. See Section B.3.3.3.2 for more information.

B.3.8.4 Summary of sensitivity analyses results

B.3.8.4.1 Probabilistic sensitivity analysis

The PSA results confirmed the findings of the deterministic analysis. The ICER, while being slightly increased, was broadly consistent with that of the deterministic analysis, showing substantial incremental health benefits in QALYs (median incremental benefit of [redacted] and mean of [redacted]). Results are summarised in Table 55 and Figure 18. Figure 19 presents the cost-effectiveness acceptability curve derived from the PSA. As shown in the figure, imlifidase was cost-effective in [redacted]% of simulations at the willingness to pay (WTP) threshold of £30,000/QALY.

Table 55 Probabilistic base case results

	Costs (£)			QALY			ICER (£/QALY)
	Imlifidase and transplant	Dialysis	Incremental	**Imlifidase and transplant**	Dialysis	Incremental	
Deterministic base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,641
PSA median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,555
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,231
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,903
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	84,857

ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year

Figure 18 Probabilistic sensitivity analysis scatter plot of imlifidase vs dialysis

[redacted]

Figure 19 Cost-effectiveness acceptability curve of imlifidase

QALY: quality-adjusted life year; WTP: willingness to pay

B.3.8.4.2 Deterministic sensitivity analysis

The results of the one-way sensitivity analysis are presented in Figure 20. In this analysis, the variable with the greatest influence on the ICER was the discount rate of the outcomes. This result is as anticipated as lower discount rates allow more weight to be given to future gains in QALYs. Therefore, lower discount rates are expected to lead to more favourable ICERs for treatments that accrue benefit in the long-term (such as for imlifidase). Similar factors are also true for the discount rate for costs. Imlifidase patients incur high cost at model entry and these costs are offset by the fact that dialysis is more expensive in the long-term; but the higher future costs are reduced by discounting relatively to the fixed initial cost of imlifidase. There are two reasons that explain the lower influence of the discount rate of costs than the discount rate of outcomes. Firstly, the costs are associated with less uncertainty and therefore, less variation in the parameter than the discount rate on the outcome. Second, because the imlifidase patients tend to have longer survival, they incur more cost toward the end of the time horizon. For a similar reason, the age of the patient at model entry plays an important role on the ICER. The younger the patients are, the longer their expected survival is, and the more time they have to accrue costs that would offset the initial cost of imlifidase. The three utility decrements all rank amongst the 11 most influential factors in the model, revealing the higher level of uncertainties associated with these parameters and their key role in driving the

ICER. The second most influential variable was the utility decrement associated with a functioning graft. The post-transplant health state is associated with higher HRQoL than the dialysis health state, and also with higher survival, hence the utility value of this health state is important in determining the QALY outcomes of the model. Finally, the proportion of patients requiring two vials of imlifidase has a direct impact on the overall cost of imlifidase, and is therefore, associated with an important impact on the ICER. A higher proportion of patients requiring two doses is associated with lower ICER because it means that less patients will require three doses.

Figure 20 Results of the one-way sensitivity analysis

AE: adverse events; AMR: antibody-mediated rejection

B.3.8.4.3 Scenario analyses

The results of the scenario analyses are presented in Table 56. The scenario analyses led to ICER values that varied between £22,163 (for a discount rate of 1.5%) and £62,857 (for a time horizon of 10 years). The impact of applying a discount rate of 1.5% (outcomes and costs) confirmed the finding from the one-way sensitivity analysis. As expected, a decrease in the time horizon, as performed in Scenario 2 and 3, led to an increase in the ICER as there were fewer years over which QALY benefits could accrue to offset the initial costs of imlifidase treatment and transplant. This is illustrated clearly in these scenarios where there were

relatively smaller differences in incremental costs and relatively larger differences in incremental QALYs. Scenario 4 explored using data from Li et al. (2017)[36] for utilities and was associated with an increase in ICER of 23%. This highlights again (as seen with the one-way sensitivity analysis) that utility inputs are an important input for this model. However, it must be remembered that these utility data from Li et al. (2017)[36] do not fully reflect the health states within this model. Scenario 5 and 6 considered alternatives estimates for graft survival predictions based on historical graft survival using the all imlifidase patient group and the 'unlikely to be transplanted' patient group, instead of the iBox model data that was used in the base case. These scenarios led to ICERs that were very close to the base case, but in both cases were slightly reduced. This shows there is robustness across these scenarios, and that the base case scenario is the most conservative approach. Scenario 7 considered the survival of patients with a functioning graft using data from the 'unlikely to be transplanted' patient group, instead of the all imlifidase data. This scenario was associated with an increase in the ICER of 53%. As outlined in Section B.3.3.3.2, this data is from a small number of patients and is driven by a small number of deaths (which were judged to not be related to imlifidase or kidney malfunction), and hence cannot be seen as a reliable estimate. The agreement between Scenarios 5 and 6 shows the similarity in clinical outcomes between the all imlifidase patient group and the 'unlikely to be transplanted' patient group, which further highlights that this difference in mortality appears to be driven by a small number of deaths in the small 'unlikely to be transplanted' patient group. Finally, the removal of a caregiver utility decrement (Scenario 8) and the change in source to Gray et al. (2019)[86] (Scenario 9) were both associated with a small change in the ICER. This shows that carer disutility is not a key driver of cost-effectiveness, but this is a factor that can be very important in the lives of patients and their carers.

Table 56 Results of the scenario analyses

	Cost difference between treatments (£)	QALY difference between treatments	ICER (£/QALY)	Difference from base case
Base case	[redacted]	[redacted]	**30,641**	–

Scenario 1: Discount of 1.5%	[redacted]	[redacted]	22,163	-28%
Scenario 2: Time horizon, 10 years	[redacted]	[redacted]	62,857	105%
Scenario 3: Time horizon, 20 years	[redacted]	[redacted]	35,676	16%
Scenario 4: Utilities from Li et al. (2017)[36]	[redacted]	[redacted]	37,612	23%
Scenario 5: Graft loss extrapolations, All	[redacted]	[redacted]	29,253	-5%
Scenario 6: Graft loss extrapolations, UT	[redacted]	[redacted]	29,556	-4%
Scenario 7: Survival extrapolations, UT	[redacted]	[redacted]	46,896	53%
Scenario 8: No caregiver disutility	[redacted]	[redacted]	31,012	1%
Scenario 9: Caregiver disutility from Gray et al. (2019)[86]	[redacted]	[redacted]	29,036	-5%

All: all imlifidase patient group; UT: 'unlikely to be transplanted' patient group

B.3.9 Subgroup analysis

No subgroups were included for consideration in this economic analysis.

B.3.10 Validation

B.3.10.1 Model quality check

Model functionality, clarity, accuracy, and consistency, model engine/Markov traces, and sensitivity analyses were validated by two external reviewers. Subsequently, these reviewers verified all numerical data included in the model. Comments and corrections were incorporated into the model.

B.3.10.2 Clinical expert model validation

The model structure, main assumptions, and data sources were presented to multiple clinical experts for validation, including experts in health economics, transplant and dialysis.

B.3.11 Interpretation and conclusions of economic evidence

The cost-effective analyses presented here demonstrate that imlifidase is a cost-effective treatment that provides long-term benefits to patients, their carers and the health system. The base case analysis yielded an ICER of £30,641 per QALY for imlifidase (with transplant) in comparison to patients who remain on dialysis (the only currently available alternative treatment for these patients). This figure constitutes a relatively conservative analysis, which is illustrated in a number of sensitivity and scenario analyses of the assumptions used in the model. In addition, various factors that would decrease the ICER of imlifidase have not been able to be included in the model (including the full impact of dialysis on patients and work productivity). Imlifidase can also be seen to be a life extending treatment that has the potential to help address some of the current inequalities in kidney transplantation.

The cost-effectiveness results for imlifidase as a desensitisation treatment for highly sensitised patients with a positive crossmatch against a deceased donor should also be considered in the context of the clinical need for an effective desensitisation treatment to allow transplantation in this group of patients where there is currently no other treatment option (other than dialysis). This identifiable unmet need further outlines the importance of imlifidase. Overall, considering all these factors, it is clear that imlifidase represents a cost-effective treatment that has substantial benefits for patients.

Treatment with imlifidase was associated with higher medical costs than were experienced by the dialysis patients. This was mainly as a consequence of the initial costs of therapy and transplant. Importantly, the overall costs of therapy are substantially offset by a reduction in costs over the long-term due to the high costs of dialysis. QALY benefits from imlifidase treatment are accrued throughout the time horizon. However, analyses with a reduced time horizon demonstrated the long-term nature of a large proportion of the QALY benefits from imlifidase (which occur due to the life extending nature of imlifidase and transplant).

The model evaluated several key areas of uncertainty in scenario and sensitivity analyses. Because imlifidase was associated with a high cost at model entry and cost offset during the following cycles, the model was particularly sensitive to

parameters that had an impact on the duration of time spent in the model (such as time horizon, patient survival and age), or on the relative importance of future earnings compared to present earning (such as discount rates). The model was also sensitive to change in the utilities. The ICERs from the scenario and sensitivity analyses ranged from £22,163 to £62,857. Many of the sensitivity analyses show that many conservative assumptions were taken in this model.

The main limitations of this economic model are related to the small population sizes in the imlifidase trials and the limited long-term data available. The populations included within the clinical trials were limited by the specialist nature of this treatment for an orphan condition. There is also the consideration that there are a limited number of kidneys available for transplant and so they are a scare resource for use within clinical trials. The lack of long-term data is due to imlifidase being a novel and innovative treatment, for which long-term follow up of treated patients is continuing (see Section B.2.11). This limitation was addressed by using a fully validated tool for the prediction of graft survival (iBox), which should help to reduce the uncertainty in this regard. Another limitation of the model is that many of the inputs are not specific to highly sensitised patients and represent a general transplant population. No data were identified that allowed the quantification of the impact of sensitisation on inputs. However, as this assumption is made across the model it is not expected to have a significant impact.

Although many dialysis-related AEs were incorporated into the model, there are other AEs, particularly related to cardiovascular events and infections that were omitted in the model due to a lack of data. This, therefore, is likely to underestimate the overall cost of dialysis. Another factor that would be expected to lead to a significant increase in the costs related to dialysis would be the inclusion of work productivity. This was excluded as it falls outside the NICE reference case, but the burdensome requirements of dialysis can have a large, detrimental impact on the lives of patients. This analysis can therefore be seen to offer a favourable analysis of dialysis compared to the reality of the patient experience.

This economic evaluation reflects the patient group identified within the decision problem and as defined by the marketing authorisation for imlifidase. The economic

analysis has been conducted with the input of UK clinical experts to ensure that this analysis reflects UK clinical practice. This analysis can therefore be considered generalisable to UK clinical practice.

Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Full study inclusion and exclusion criteria

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Clarification questions

28 September, 2020

File name	Version	Contains confidential information	Date
ID1672_Imlifidase_ERG Clarification_Hansa response	1.0	No (redacted)	16 October 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Literature searches

A1. Please confirm that searches for clinical effectiveness and for adverse events were combined together into one search strategy and one set of search results? [Appendix D]

Search A, as detailed in Appendix D, was a combined search focussing on both clinical effectiveness and safety (adverse events). The results for clinical effectiveness and for adverse events are therefore included in the one set of search results from Search A.

A2. Please confirm that clinical effectiveness/adverse events search results were limited to RCTs for study type? What was the rationale for this? [Appendix D]

The search results for clinical effectiveness and adverse events (Search A) were limited to all relevant study designs, not solely randomised controlled trials (RCTs). In addition to RCTs, other study types including meta-analyses, systematic literature reviews, observational studies, databases and registries were included, as detailed in Appendix D. These search terms utilised to limit Search A to these relevant designs were based on strategies and search filters created by the Scottish Intercollegiate Guidelines

Network (Available at: https://www.sign.ac.uk/what-we-do/methodology/search-filters/) and the Cochrane Collaboration (Available at: https://work.cochrane.org/rct-filters-different-databases). The rationale for these decisions was to attempt to identify all relevant sources of evidence, whether or not these were RCTs.

Systematic review methods

A3. Please can you clarify whether the domain and summary quality appraisal ratings using ROBINS-I (CS Document B, p.61) applied to all study outcomes reported in the CS? How were summary ratings derived (i.e. was this based on a count/threshold of domain-specific items, or was the relative weight of items taken into consideration)?

The domain quality appraisal ratings using the ROBINS-I apply to all study outcomes for each of the four included studies. The responses to individual signalling questions provided the basis for domain-level judgements about risk of bias, which then provided the basis for an overall risk of bias judgement. The ROBINS-I tool provides clear guidance and criterion on the interpretation of domain-level judgements to form an overall risk of bias. For example, a study is classed as an overall low risk of bias only if the study is judged to be at low risk of bias within all domains and a study is classed as having a moderate risk of bias only if there is a low or moderate risk of bias for all domains.

A4. With regard to the quality assessment of the 4 included studies using ROBINS-I reported in Appendix D, can you please provide further clarification on the following?

- **What were the important confounding factors relevant to the studies that were considered in the quality assessment?**
- **On what basis was a 'probably yes' rating given to the items regarding appropriate analyses to account for confounding/time-varying confounding?**

Confounding factors are not expected to have a significant impact on the primary study outcomes and the main outcomes related to the ability for a transplant to be conducted (elimination of donor specific antibodies (DSAs) and crossmatch conversion). There is no evidence that Hansa is aware of that identifies any significant confounding factors in relation to these endpoints. However, as literature in this area is not extensive, Hansa believed that it was not plausible or reasonable to assume that there was no potential for confounding. Hansa believes that based on the available evidence there is only a very low risk of bias within these endpoints. Any confounding factor within these studies is more likely to become apparent in endpoints related to long-term outcomes of the kidney transplant. Potential confounding factors in this area were considered during the quality assessment (including, for example, cold ischaemia time, time on dialysis and age).

An answer of 'probably yes' was given to the items regarding appropriate analyses to account for confounding as these areas were considered during the conduct of the study. As mentioned above, the primary endpoints were not judged to be at risk from known confounding factors, and so no additional analyses were considered. As the other endpoints that were at a higher risk of influence from confounding factors were secondary outcomes, less detail on analyses on these endpoints was included and reported within the study reports. This lack of detail within the study reports led Hansa to believe that an answer of 'probably yes' was the most appropriate response, as full details were not included in this area. Hansa is aware that the impact of confounding factors was considered during the conduct of this study, but the ability to conduct analyses to account for any confounding was limited by the size of these trials. In addition, to attempt to mitigate any confounding, post-hoc stratification analyses were undertaken. Overall, this was felt to justify the rating given in this regard.

A5. Please can you comment on the quality (i.e. risk of bias) of your analyses using the combined population set of patients unlikely to receive a transplant taken from across the 4 studies? What do you think are the key limitations of these analyses for informing the decision problem?

For the analyses using the combined populations, the overall risk of bias can be seen to be equivalent to that of the individual trials, with a moderate overall risk of bias. The main potential source of bias in this dataset remains the risk of confounding. However, as discussed above, there is no evidence that Hansa is aware of which identifies any significant confounding factors in relation to the main and primary endpoints of these analyses (elimination of DSAs and crossmatch conversion; these primary endpoints were chosen as they are objective and quantifiable across all patients). The larger size of the combined dataset is beneficial and has allowed further post-hoc stratification analyses to be conducted, such as the 'unlikely to be transplanted' group. This focussed on the most relevant patients for this appraisal and so reduced the potential risk of bias for longer term outcomes (where the risk of confounding factors was higher) that may have occurred due to the influence of any other patients included within the trials.

The 'unlikely to be transplanted' group is the most relevant population for addressing the decision problem, as it best reflects the population of patients that would be expected to be treated in UK practice. There are no key limitations within these data beyond those of wider trials. The main key limitations in this combined data are therefore the size of the dataset (the patient numbers treated remain limited even within this combined analysis due to the nature of this orphan indication) and the non-randomised/controlled nature of the clinical trials (ethical and practical barriers exist to be able to conduct a randomised and controlled trial in this area). These are the best available data on which the efficacy of imlifidase can be judged, and to inform the decision problem.

Clinical effectiveness evidence

A6. Please clarify that the scoped outcomes of time to next renal replacement therapy, proportion of patients requiring treatment of rebound antibodies following transplant, and hospitalisation days are not reported in the submission.

The aforementioned scoped outcomes of time to next renal replacement therapy and hospitalisation days are not reported within the submission. These outcomes were not stated outcomes for any of the included clinical trials. There are therefore no data available to be presented in relation to these outcomes. In addition, the length of the studies and the number of subjects included, would not allow any estimations of the expected time to next renal replacement to be made at the current time.

In terms of the proportion of patients requiring treatment of rebound antibodies following transplant, again, this was not a directly defined outcome for any of the included clinical trials. However, it can be noted that all transplanted patients received immunosuppressive treatment to prevent rejection of the kidney (but not with the express intention of treating rebound antibodies). In addition, amongst the 46 transplant recipients during the clinical trials of imlifidase, 15 (33%) had at least one episode of antibody-mediated rejection (AMR). Within the target population, 10 of the 25 patients showed signs of AMR. All patients with AMR were successfully treated with standard, centre-specific immunosuppressive protocols, and were within the range cited within literature for comparable patient groups. No additional analysis was undertaken to quantify any rebound antibodies, and decisions related to treatment of AMR were related to the clinical presentation of this condition and not any analysis of rebound antibodies. These data provide some context of the queried outcome, but do not provide sufficient data to provide any firm figures in this regard.

A7. Please clarify what proportion of patients across all studies deemed unlikely to receive a transplant according to the definition provided (cPRA of ≥95% [MFI ≥3000] and positive crossmatch, without regard to deceased donor transplant)

actually received a) a transplant from either deceased or living donor; b) a transplant from a deceased donor.

Within the population of 25 patients presented within the submission as the 'unlikely to be transplanted' group, all 25 patients (100%) received a transplant from a deceased donor after imlifidase treatment and all transplants were successfully carried out. This group of patients included only patients who received a deceased donor transplant, as this matches the marketing authorisation for this product. This decision was made in order for the 'unlikely to be transplanted' group to best represent the marketing authorisation and the patient group under consideration within this appraisal with respect to this aspect (receiving a kidney from a deceased donor).

A8. Could you please provide the following information for the patients who are described as unlikely to receive a transplant in your combined analysis?

- **The proportion of patients who received imlifidase under the dosage approved as part of marketing authorisation.**
- **The IQR and/or range of time on dialysis for included patients**
- **The proportion of patients who you consider would be consistent with the marketing authorisation for imlifidase and the population in the UK who would be eligible for treatment.**

Within the 'unlikely to be transplanted' group, 96% (24/25) received a dosage of imlifidase consistent with the marketing authorisation (i.e. 0.25mg/kg or 0.24mg/kg, which were considered equivalent). In the wider group of transplanted patients, 87% (40/46) received a dosage consistent with the marketing authorisation. Patients who did not receive a dosage consistent with the marketing authorisation generally received a dose of 0.50mg/kg as part of the dose finding aspects of the clinical trials (which is equivalent to the licensed dose for those patients who require a second dose at 0.25mg/kg).

For the patients within the 'unlikely to be transplanted' group, the time to dialysis ranged from [redacted] to [redacted] years, with an interquartile range (IQR) of [redacted] years.

The population selected for the 'unlikely to be transplanted' group were those patients deemed most relevant to receive imlifidase across different allocation systems in European countries. Entry into this group was defined by patients that met all three of the following criteria:

- calculated panel-reactive antibodies (cPRA) of ≥95% (mean fluorescence intensity [MF]I ≥3000)
- deceased donor transplant, and
- a positive crossmatch to potential donor organ.

The marketing authorisation restricts the use of imlifidase to patients who are highly sensitised, with a positive crossmatch to an available deceased donor kidney; with a recommendation that the use of imlifidase is reserved for patients unlikely to be transplanted (with consideration of current kidney allocation system and prioritisation programmes). All patients included within the 'unlikely to be transplanted' group are consistent with the marketing authorisation of imlifidase, as only patients with a cPRA of ≥95% (higher than the UK threshold for consideration as a highly sensitised patient) and a positive crossmatch to a deceased donor kidney were included in this group. The definition of whether a patient can be considered unlikely to be transplanted is a more subjective judgement based on a number of considerations for an individual patient (including the human leucocyte antigen [HLA] antigen profile and potential match to a donor, how long the patient has been on dialysis, how sick the patient may be etc.) and not just on the cPRA value. Through discussion with UK clinical experts, it was clear that within the group of highly sensitised patients (cPRA/calculated reaction frequency [cRF] ≥85%) there was still a chance of transplant for the vast majority of patients in the range 85–95%. However, with a cPRA ≥95% there is a substantial increase in patients that would be considered as unlikely to receive a transplant. When considering the likelihood of transplant, it must also be remembered that there is a limited supply of donor organs, which restricts transplant opportunities for all patients; however, the impact of this, often, most heavily falls on patients with a high degree of sensitisation. While the recent changes to the UK Kidney Offering Scheme (KOS) aimed to increase transplant for highly sensitised patients, this benefit does not extend to all highly

sensitised patients some of whom remain unlikely to receive a transplant. The highly sensitised patients who receive the largest benefit from the updated scheme are those in Tier A of the KOS, which includes patients with a matchability score of 10, or those who have been on the waiting list for 7 years or more. However, there are some patients within Tier B who remain highly unlikely to receive a transplant. Overall, it can be seen that the definition of the 'unlikely to be transplanted' group also matches with patients that are unlikely to be transplanted in UK clinical practice. All patients within this 'unlikely to be transplanted' group can be seen to be within the marketing authorisation and all of the 'unlikely to be transplanted' group can be seen to be equivalent to UK patients that would be expected to receive this treatment. Within the UK, Hansa expects that the group of patients eligible for imlifidase would include all highly sensitised patients (with a cPRA ≥85%) that are unlikely to receive a transplant through other means.

In addition, it should be noted that Hansa believes that a small subgroup of eligible patients that may receive imlifidase fall outside the 'unlikely to be transplanted' group. This consists of individual patients with a sensitisation in the range 85–95% but have a particular immunological profile that makes them unlikely to receive a transplant (e.g. high total MFI load and/or a number of problematic DSAs). This expectation was shared by UK clinical experts consulted by Hansa. These patients will need to be identified by clinicians based on an individual assessment. Therefore, these patients were not attempted to be included within the 'unlikely to be transplanted' group, as it raised the possibility of a selection bias if the group was not defined using clear and objective measures. The criteria chosen were therefore taken as a balance to recognise that there was no hard cut-off in cPRA that corresponded to a patient being unlikely to be transplanted. Below a cPRA of 95%, it can be seen that the vast majority of patients would not be eligible for imlifidase (with some exceptions); but at a cPRA of 95% or above, there is a substantial increase in the proportion of patients who would be considered eligible for imlifidase. The definition of this group was also chosen to cover varying definitions of highly sensitised and priority programmes/allocation systems across many countries.

Hansa wishes to be clear that imlifidase is a highly specialised treatment for patients with the greatest need, and that it remains the case that only a minority of patients with cPRA ≥95% would be considered eligible for imlifidase. A cPRA of 95% represents a value where there is a substantial increase in eligible patients for imlifidase. This justifies the choice of this figure as an objective cut-off despite it not corresponding to any particular guideline or specific clinical practice, with the caveat that this value does not cover all imlifidase eligible patients (some of whom are likely to have a cPRA of less than 95%).

Hansa would also like to confirm again the details and differences between cPRA and cRF. Within UK clinical practice cRF is the standard measure that is used, and the cRF is the percentage of 10,000 recent UK donors that the patient has pre-formed antibodies against and is measured when patients are listed for transplant. The cPRA is a measure that is used commonly outside the UK, which is a computer-based method to test the reactivity of the patient's antibody profile against the HLA profile of >12,000 potential donors. So, whilst there are clear similarities between these measures in how sensitisation is quantified, differences in the panel of donors used for comparison means that these two measures cannot be considered identical. This adds further weight to the application of clinical judgement to individual cases within the UK, as there may be minor variations between cPRA and cRF values. Additionally, the cut-off used by Hansa in the 'unlikely to be transplanted' analyses ensured that the patients chosen would still sit within the definition of highly sensitised whether defined by cPRA or cRF.

A9. Please clarify which trials, if any, used the virtual crossmatch test that is standard in UK practice.

The type of crossmatch test used in each of the trials was as follows: 13-HMedIdeS-02 and 14-HMedIdeS-04 only fluorescence-activated cell sorting (FACS) crossmatch tests were monitored and recorded, 13-HMedIdeS-03 used FACS and complement dependent cytotoxicity (CDC) crossmatch tests and 15-HMedIdeS-06 used FACS, CDC and virtual crossmatch tests. In all of the clinical studies virtual crossmatch tests were

not used to decide whether to transplant or not, and FACS or CDC crossmatch tests were used in all patients.

Hansa wishes to clarify the usage of crossmatch tests within the UK, and the main differences between these crossmatch techniques. The CDC and FACS crossmatch tests are physical tests that require blood samples from both the donor and recipient. The CDC crossmatch tests lymphocytes from the donor and are mixed with recipient serum, alongside complement (the immune component) and judges the crossmatch based on cell lysis. This is the oldest and least sensitive of the crossmatch tests, but retains its importance and use as a complement activating reaction can be often seen to be predictive of a poor transplant outcome. The FACS crossmatch test is a more sensitive revision of the CDC test, and uses donor lymphocytes and recipient serum, which are mixed with fluorescently labelled antibodies directed against human immunoglobulin G (IgG). A crossmatch in this test results from any detectable binding of labelled antibodies to DSAs that have bound to the donor lymphocytes. The virtual crossmatch (as the name implies) relies upon a virtual consideration of the crossmatch. This is achieved by producing HLA profiles of both donor and recipient using the single antigen bead (SAB) assay. These HLA profiles can then be compared to identify potential positive crossmatches based on this HLA profile. As HLA profiling is carried out routinely at entry onto the transplant list, this allows virtual crossmatch tests to be conducted for new available donor organs as they become available.

The virtual crossmatch is therefore standard within UK clinical practice as an initial and rapid tool for the evaluation of crossmatch between donor and recipient. This has the particular advantage that as physical samples from the donor and recipient are not required in the same location, the virtual crossmatch can be used as a screening tool to quickly find potential negative crossmatch recipients for a donor organ. The British Transplantation Society Guidelines on "*The detection & characterisation of clinically relevant antibodies in allotransplantation*" (Available at: https://bts.org.uk/wp-content/uploads/2016/09/06_BTS_BSHI_Antibodies-1.pdf) provide more detail in this regard, and on the usage of virtual crossmatch tests. These guidelines note that

"*Patients with no antibodies, or those with fully defined HLA-specific antibodies can be transplanted without a prospective laboratory crossmatch test provided the virtual crossmatch is negative i.e. the donor does not carry those HLA specificities to which the patient is sensitised*". This means that transplants may proceed on the strength of a negative virtual crossmatch (although the guidelines also state that a retrospective laboratory crossmatch test should be performed in these cases). However, as these guidelines note, patients who have positive virtual crossmatches and more complex cases (as would be the case for all imlifidase patients) should have laboratory crossmatch tests conducted (i.e. CDC and/or FACS crossmatch tests). So whilst a virtual crossmatch test will be used for initial evaluation of a potential transplant, in the case of imlifidase, additional tests (most likely FACS crossmatch tests) will also be conducted in order to allow for a transplant to proceed.

A10. Please confirm what proportion of patients a) across all included studies, b) in the Jordan 2017 analysis, c) in the combined analysis of most relevant patients did not experience conversion to negative crossmatch after imlifidase dosing.

The proportion of patients who did not experience conversion to negative crossmatch after imlifidase dosing was:

a) The determination of a crossmatch requires a donor to be compared against a potential recipient. Therefore, the conversion to a negative crossmatch cannot include the patients within trial 13-HMedIdeS-02 since it was primarily designed to find the appropriate imlifidase dose to eliminate anti-HLA antibodies. Transplantation was not part of the trial, but for one patient an HLA-incompatible organ became available. Imlifidase converted both CDC and FACS crossmatch tests to negative and the patient was transplanted. The trial 13-HMedIdeS-02 did include an analysis of crossmatch conversion against several hypothetical donors. However, this was conducted as an academic analysis and so is not considered in response to this question as it was carried out after the event and did not influence clinical practice during the trial (such as through a re-dosing of imlifidase), which might occur with the prospect of a real transplant. Therefore, these data were not considered clinically applicable.

This resulted in a population of the 46 transplanted patients plus the patient in trial 15-HMedIdeS-06 who discontinued after a partial dosing of imlifidase. 4% (2/47) of these patients across all included studies did not experience a conversion to negative crossmatch after imlifidase treatment. One of these patients (in trial 15-HMedIdeS-06) received only a partial total dose of approximately [redacted] before imlifidase was withdrawn, and the patient was withdrawn from the trial. The second patient (also in trial 15-HMedIdeS-06) was borderline flow crossmatch positive but virtual crossmatch negative after imlifidase treatment, this was judged as not clinically significant and the transplant was successfully carried out. It is noted that some patients required a re-dosing of imlifidase in order to achieve crossmatch conversion, where a positive crossmatch result occurred after the initial dosing with imlifidase.

b) 0% (0/25) in the Jordan 2017 analysis.

c) 4% (1/25) in the combined analysis of the most relevant patients. This patient (in trial 15-HMedIdeS-06) had a borderline flow crossmatch and negative virtual crossmatch after imlifidase, which was judged as not clinically significant and transplant was successfully carried out.

A11. Please provide additional baseline characteristics for all of your analysis samples to include: time on dialysis; number of previous transplants; previous pregnancy; incidence of previous positive crossmatch (where not already provided in the CS)

Additional baseline characteristics that were collected are detailed in the tables below split by trial and by combined analysis group.

Table A11.1 Additional baseline characteristics of imlifidase clinical trials

	13-HMedIdeS-02 (n=1)	13-HMedIdes-03 (n=10)	14-HMedIdeS-04 (n=17)	15-HMedIdeS-06 (n=19)
Time on dialysis Mean(SD); Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
No. of previous transplants Mean; Median	[redacted]	[redacted]	[redacted]	[redacted]

SD: standard deviation

	All transplanted patients (n=46)	'Unlikely to be transplanted' (n=25)
Time on dialysis; Mean(SD); Median (range)	[redacted]	[redacted]
No. of previous transplants Mean; Median	[redacted]	[redacted]

SD: standard deviation

Information on previous pregnancy is not available within the clinical data held by Hansa. Information cannot be provided on the incidence of previous positive crossmatch. The reason being, crossmatch tests are conducted at the time when a potentially suitable donor organ is available; therefore, patients on the transplant waiting list database can experience numerous positive crossmatch predictions, which are not necessarily recorded and thus these data were not collected and is not available to present. A full crossmatch testing procedure will only be conducted where a transplant is expected to be able to occur; however, data on previous positive crossmatch tests or virtual calculations were not recorded during the trials of imlifidase.

A12. Please provide aggregated adverse event data for patients across the 4 samples who (a) received a dose of imlifidase and (b) meet the target population criteria for the appraisal.

Table 23 within the company submission summarised the adverse events for all 54 patients who received a full or partial dose of imlifidase across the four clinical trials of imlifidase. These data are also split between those who received a transplant and those

who did not, as higher rates of adverse events were seen following transplant due to transplant-related treatments and events. This is reproduced below as Table A12.1.

Table A12.1 Summary of adverse events

Patients experiencing the following	Transplanted (n = 46)	Not transplanted (n = 8)	Total safety set (n = 54)
≥1 AE	46 (100.0%)	8 (100.0%)	54 (100.0%)
≥1 TEAE	46 (100.0%)	8 (100.0%)	54 (100.0%)
≥1 treatment-related AE	13 (28.3%)	7 (87.5%)	20 (37.0%)
Any mild AE	3 (6.5%)	3 (37.5%)	6 (11.1%)
Any moderate AE	3 (6.5%)	1 (12.5%)	4 (7.4%)
Any severe AE	5 (10.9%)	3 (37.5%)	8 (14.8%)
Any life-threatening AE	2 (4.3%)	0	2 (3.7%)
≥1 treatment-related TEAE	12 (26.1%)	7 (87.5%)	19 (35.1%)
Severe treatment-related TEAE (non-SAE)	3 (6.5%)	0	3 (5.6%)
Fatal AE	0	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

The aggregated adverse event data for the 'unlikely to be transplanted' target population is presented in Table A12.2.

Table A12.2 Summary of adverse events for combined analysis groups

Patients experiencing the following	'Unlikely to be transplanted' (n=25)	All Transplanted patients (n=46)
≥1 AE	25 (100.0%)	46 (100.0%)
≥1 TEAE	25 (100.0%)	46 (100.0%)
≥1 treatment-related AE	5 (20.0%)	13 (28.3%)
≥1 treatment-related TEAE	5 (20.0%)	12 (26.1%)
Severe treatment-related TEAE (non-SAE)	1 (4.0%)	3 (6.5%)
≥1 TEAE leading to study discontinuation	0	0
≥1 TEAE leading to treatment discontinuation	0	0
Fatal AE	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

A13. Please could the company confirm the number of patients who (a) received imlifidase and (b) received imlifidase with the intention to transplant, were unable to receive the therapeutic dose due to adverse events, and thus did not achieve a conversion to negative crossmatch. We believe the figures to be [redacted] and [redacted]

The number of patients who received imlifidase, but were unable to receive the full therapeutic dose due to adverse events was 2/54. This included one patient in 13-HMedIdeS-02 due to receive 0.25mg/kg, but the infusion was stopped [redacted]. As this patient was part of the trial 13-HMedIdeS-02 where transplant was not a predefined part of the trial, there was no donor with which to judge a crossmatch and so no conclusion can be drawn on whether this partial dosing would have prevented crossmatch conversion. There was also one patient in 15-HMedIdeS-06 who received a partial dose of approximately [redacted] before imlifidase was withdrawn due to adverse events.

The number of patients who received imlifidase with the intention to transplant, but were unable to receive the full therapeutic dose due to adverse events was 1/47 (46 patients were transplanted plus the one patient who did not receive the full dose). This one patient was the aforementioned patient in 15-HMedIdes-06.

A14. Please provide aggregated quality of life data using the KDQOL-SF for patients across 13-HMedIdeS-0 who 15-HMedIdeS-06 who (a) received a dose of imlifidase and (b) meet the target population criteria for the appraisal

Health-related quality of life data were not collected as part of the initial clinical trials for imlifidase (13-HMedIdes-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06) and thus no data are available to be presented within the company submission. A longer term study, which is currently ongoing (17-HMedIdeS-14), is collecting quality of life data from imlifidase treated patients. Data from this study are not yet available.

A15. 10 of the 25 patients (CS Document B p.85) identified as the target population showed signs of antibody-mediated rejection; is this rate higher or lower than would be expected in a renal transplant in general?

The AMR rate of 40% (10/25) experienced by the target population is comparable to the rate of 33% (15/46) experienced by all 46 patients that received a renal transplant within the four clinical trials included in the submission. All patients who experienced AMR were successfully treated using centre-specific protocols.

The frequency of AMR in highly sensitised patients treated with imlifidase is similar to the frequencies reported in the literature for sensitised patients who are desensitised and then transplanted (24–61%, Table A15.1). It must be noted that this was considered the most comparable data within the literature, but that as imlifidase patients were previously considered untransplantable there is no directly comparable data for deceased donor transplants with patients of this degree of sensitisation and DSAs. These studies included both living and deceased donors, but there was no clear differences in rates within these figures.

Table A15.1 Literature rates of antibody-mediated rejection in desensitised patients

Reference	Type of donor	AMR incidence
Lefaucheur et al. 2008[1]	Deceased (93%) and living (7%) donors	28%
Magee et al. 2008[2]	Deceased (3%) and living (97%) donors	39%
Thielke et al. 2009[3]	Living donors	24%
Gloor et al. 2010[4]	Living donors	41%
Riella et al. 2014[5]	Living donors	61%
Vo et al. 2008[6]	Deceased (37%) and living (63%) donors	25%

1. Lefaucheur C, Suberbielle-Boissel C, Hill GS, et al. Clinical relevance of preformed HLA donor-specific antibodies in kidney transplantation. Am J Transplant 2008; 8: 324–331.
2. Magee CC, Felgueiras J, Tinckam K, et al. Renal transplantation in patients with positive lymphocytotoxicity crossmatches: One center's experience. Transplantation 2008; 86: 96–103.
3. Thielke JJ, West-Thielke PM, Herren HL, et al. Living donor kidney transplantation across positive crossmatch: The University of Illinois at Chicago experience. Transplantation 2009; 87: 268–273.
4. Gloor J, Stegall MD. Sensitized renal transplant recipients: Current protocols and future directions. Nat Rev Nephrol 2010; 6: 297–306.

5. Riella LV, Safa K, Yagan J, et al. Long-term outcomes of kidney transplantation across a positive complement-dependent cytotoxicity crossmatch. Transplantation 2014; 97: 1247–1252.
6. Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. New Engl J Med 2008; 359: 242–251.

A16. Where a clinician predicts high risk of long-term donor specific antibodies (DSAs), how frequently would long-term DSA monitoring be employed? Please provide the cost of a DSA test within the NHS.

The BTS guidelines on "The detection & characterisation of clinically relevant antibodies in allotransplantation" (Available at: https://bts.org.uk/wp-content/uploads/2016/09/06_BTS_BSHI_Antibodies-1.pdf) state that for patients who have undergone some form of desensitisation, it is recommended that DSA testing should be performed at least once in the first year post-transplant and when antibody production may be suspected.

Transplant specialists in the UK have informed Hansa that the frequency of DSA monitoring would be expected to broadly follow the same schedule as other kidney transplants. As there are no set guidelines in this area clinical practice appears to vary by centre. However, the experts consulted agreed that tests would only be carried out when a problem with antibody development is suspected for any kidney transplant recipient. The experts also agreed that monitoring would occur most intensively in the period following transplant, but that this would step down over time.

The most detailed response received from a clinical expert stated that the frequency of surveillance DSA monitoring would depend on the graft function. If the transplant function was stable, a DSA test would be done weekly for the initial four weeks, and then less frequently (fortnightly or monthly) over the next 2–6 months. When imlifidase was being used, there was an expectation that this testing schedule would be delayed for a week to allow for the IgG to reform. Hansa believes that it would be prudent for monitoring of DSAs to continue over at least 12 months in patients who have received imlifidase. However, in the event of graft dysfunction (at any time point for any kidney transplant recipient), reactive testing of DSA levels will occur; the frequency of this

reactive testing depends on how well the kidney is functioning and may never be required.

The cost of a DSA test for determination of an individual HLA antigen is approximately £55 per antigen (Leicester General Hospital, Transplant Laboratory Service User Manual; Available at: https://www.leicestershospitals.nhs.uk/EasysiteWeb/getresource.axd?AssetID=75939&type=full&servicetype=Attachment), and this cost was verified by consultation with UK clinical experts. In imlifidase patients it would be expected that there may be around three antigens of interest, although this may vary between one and six. The number of antigens requiring analysis will vary on a patient-by-patient basis and will be done as needed.

A17. Would a crossmatch test be required after each vial of imlifidase to confirm negative crossmatch?

No, a crossmatch test would only be required once a patient has received the full dose of imlifidase (0.25mg/ml). Once the full dose has been administered, there would be a requirement to wait 2–6 hours with a crossmatch test then conducted.

A18. How does the company expect cold ischaemic time to be affected by a requirement for (multiple) CDC tests following imlifidase vial(s)?

Multiple CDC tests will not be required following imlifidase vials, and only a single crossmatch test following the full dose of imlifidase is required. The SmPC states that crossmatch conversion should be confirmed after imlifidase treatment, but does not specifying what type of test is required (CDC or FACS).

Hansa expects that, following administration of imlifidase, there will be a 2–6 hour wait for imlifidase to act, followed by a crossmatch test. Based on consultation with clinical experts, Hansa expects that this would lead to a total of approximately 6–8 hours between imlifidase administration and transplant. The Organ Donation and Transplantation Activity Report 2019/20 produced by NHSBT (Available at:

https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/19220/activity-report-2019-2020.pdf) shows a current median cold ischaemic time of 12 hours for donation after circulatory death (DCD) and 13 hours donation after brain death (DBD) transplants.

A19. Please confirm that rates of malignancies are not included in the submission's discussion of adverse events.

No trial emergent malignancy was reported during the trials, and rate of malignancies was consequently not discussed in the discussion of adverse events.

A20. Please clarify the reasoning for the use of cPRA of ≥95% in the definition of 'highly sensitised' rather than the commonly accepted value of cPRA of ≥85%.

Hansa does not seek to use an alternative definition for 'highly sensitised' within this appraisal, and agrees that the commonly accepted value is cPRA/cRF of ≥85%.

Within the analysis of the most relevant population to UK clinical practice, the 'unlikely to be transplanted' group included a criterion of a cPRA of ≥95%. This group also had the additional criteria of requiring a deceased donor kidney offer and positive crossmatch test. The definition of this group was chosen to cover varying definitions of highly sensitised and priority programmes across many allocation systems. The group therefore broadly matches the product licence and the expected UK usage of this product. Hansa Biopharma AB also believes that as there is not an accepted definition for this patient group of unlikely to be transplanted patients, that the decision to treat with imlifidase should be left to the treating physician's discretion. The definition of whether a patient can be considered unlikely to be transplanted is a subjective clinical judgement based on a number of considerations for an individual patient. Through discussion with UK clinical experts, it was clear that within the group of highly sensitised patients (cPRA/cRF ≥85%) there was still a chance of transplant for the vast majority of patients in the range 85–95%. However, a cPRA/cRF of ≥95% led to a substantial increase in the proportion of these patients considered unlikely to receive a transplant. The criteria chosen in this regard were not tied to any particular guideline or specific

clinical practice, and were used purely to define a population for this analysis which matches the expected patient population.

In addition, it should be noted that Hansa believes that a small subgroup of eligible patients that may receive imlifidase fall within the sensitisation range of 85–95% (and therefore within Tier B of the UK KOS, and so would not benefit from priority consideration for a transplant). This consists of individual patients with a sensitisation in the range 85–95% but have a particular immunological profile that makes them unlikely to receive a transplant (e.g. high total mean fluorescence intensity [MFI]-load and/or a number of problematic DSAs). This also demonstrates how cPRA cannot be seen as the sole factor in determining likelihood of transplant and how a wide range of factors (including the HLA antigen profile and potential match to a donor, how long the patient has been on dialysis, how sick the patient may be etc.) influence this clinical decision. This view was shared by UK clinical experts consulted by Hansa. These patients with a sensitisation in the range 85–95% will need to be identified by clinicians based on an individual assessment. The criteria chosen were therefore taken as a balance to recognise that there was no hard cut-off in cPRA that corresponded to an individual patient being considered unlikely to be transplanted. Below 95% cPRA, it can be seen that the vast majority of patients would not be eligible for imlifidase (with some exceptions); but at 95% cPRA or above, there is substantial increase in the proportion of patients that would be considered eligible for imlifidase. This justifies the choice of this figure as a cut-off for cross regional/cross allocation system discussion of highly sensitised patients who are unlikely to be transplanted, despite it not corresponding to any particular guideline or specific clinical practice, and, with that, this value does not cover all imlifidase eligible patients (some of whom are likely to have a cPRA of less than 95%).

Hansa would also like to confirm, again, the details and differences between cPRA and cRF. Within UK clinical practice cRF is the standard measure that is used, and the cRF is the percentage of 10,000 recent UK donors that the patient has pre-formed antibodies against and is measured when patients are listed for transplant. The cPRA is a measure

that is used commonly outside the UK, which is a computer-based method to test the reactivity of the patient's antibody profile against the HLA profile of >12,000 potential donors. So, whilst there are clear similarities between these measures in how sensitisation is quantified, differences in the panel of donors used for comparison means that these two measures cannot be considered identical. This adds further weight to the application of clinical judgement to individual cases within the UK, as there may be minor variations between cPRA and cRF values.

Section B: Clarification on cost-effectiveness data

B1. Please can the company confirm the pack sizes of imlifidase that will be made available in the UK? The submission repeatedly lists a price per vial, however the economic model uses a price for two vials (which is then divided by two to give a price for one vial). Will the pack be of one or two vials?

Imlifidase will be supplied in packs of one and two vials, which will both be made available in the UK. As can be seen within the economic model, it is expected that the majority of patients will require two vials in order to receive the indicated dosing of 0.25mg/kg. The two vial pack will supply this, and so during the development of the economic model, this was assumed to be the 'standard' pack size. However, packs of one vial will also be available to give full flexibility in purchasing, and Hansa can confirm that the per vial price will be identical between the two pack sizes. Therefore, for simplicity, a per vial price was referred to within the company submission.

B2. Jordan et al. (cited in the company submission) state that 'only 6.5% of patients with a panel reactive HLA antibody (PRA) levels above 80% [i.e. highly sensitized (HS)] receive a transplant each year'. What percentage of patients with higher sensitization levels (i.e. >95% as used in the company submission) would the company estimate receive a transplant each year in the absence of imlifidase?

(Jordan, Stanley C. Choi, Jua, Vo, Ashley. Kidney transplantation in highly sensitized patients, British Medical Bulletin, 2015, Vol 114, Issue 1, p.113-125)

The Jordan et al. publication referenced above refers to US data prior to changes to the Kidney Allocation Scheme (KAS) in that country. These changes were made with the aim of increasing access to transplant for patients with the highest cPRA levels. Recent publications have shown that these changes have increased transplantation for the patients with the highest cPRA levels, and hence will have altered the proportion compared to that reported in the Jordan et al. publication.

The UK has now made changes their KOS with similar aims to the US, and so improvements in the proportion of the most highly sensitised patients in the UK receiving a transplant should also be expected (and is starting to be seen). However, it is expected that these changes will not perhaps be to the same levels as in the US, since the donor pool is smaller in the UK. Also, although the changes to the KOS are expected to increase the access to transplant for some highly sensitised patients, this benefit will not extend to all patients. The estimation of a proportion of highly sensitised patients who would receive a transplant without imlifidase is challenging with these recent changes to the KOS and due to the limited published data that are available within this area. Based on this, Hansa do not feel in a position to provide an estimate for this value.

In addition, Hansa note that patients eligible for imlifidase are those who are expected to be unlikely to receive a transplant without imlifidase treatment. Hansa have provided estimates as to the proportion of highly sensitised patients that would be unlikely to receive a transplant within the updated KOS (and hence are eligible for imlifidase). The proportion of the remaining patient population that actually receive a transplant each year is dependent upon availability of suitable organs (which is limited). However, as these patients receive a transplant they would not have been considered as potential imlifidase patients. Therefore, Hansa does not believe that this is directly relevant to this appraisal which is focussed on the subgroup of patients who are unlikely to receive a transplant without imlifidase treatment.

B3. Could you please clarify the characteristics (including age) of the 'all-patients' sample used for survival extrapolation? Has any adjustment been made so that the extrapolation matches patient baseline characteristics within the model?

The category of 'patient survival with a functioning graft' used the full sample of patients in the 'all imlifidase' group (n=46). No adjustments were performed on these data as the mean age of the 'all imlifidase' patients was 43.4 years old, which closely matched the age at model entry of 45 years old.

B4. With respect to the description of the survival analysis aspects of the economic model, could the company confirm 'all imlifidase' refers to all imlifidase patients who received a transplant, and not all patients who received a dose of imlifidase (regardless of subsequent transplant)?

Within the survival aspects of the economic model, the 'all imlifidase' group refers to all 46 patients who received treatment with imlifidase and a subsequent transplant.

B5. Could the company please clarify the characteristics (including age) of the patients that were analysed using the iBox graft survival prediction tool? Please could the company provide the relevant materials and inputs to allow the ERG to replicate the analysis performed with iBox.

The characteristics of the patients analysed using the iBox graft survival prediction tool are summarised in the Table B5.1.

Table B5.1 iBox patient characteristics

Age (years)	**Mean (SD)**	[redacted]
	Range	[redacted]
Sex, n (%)	**Female**	[redacted]
	Male	[redacted]
Race, n (%)	**White**	[redacted]
	Black	[redacted]
	Other	[redacted]
Weight (kg)	**Mean (SD)**	[redacted]
	Range	[redacted]
Body mass index	**Mean (SD)**	[redacted]

	Range	[redacted]
Mean time on dialysis before transplant (years)	**Mean (SD)**	[redacted]
Hepatic impairment at inclusion	**n (%)**	[redacted]
Cardiovascular disease at inclusion	**n (%)**	[redacted]
Diabetes at inclusion	**n (%)**	[redacted]
Autoimmune disorder at inclusion	**n (%)**	[redacted]
Number of previous renal transplants	**0, n (%)**	[redacted]
	1, n (%)	[redacted]
	2, n (%)	[redacted]
	3, n (%)	[redacted]
Deceased donor status	**n (%)**	[redacted]
Organ storage	**Simple cold storage, n (%)**	[redacted]
	Hypothermic machine perfusion, n (%)	[redacted]
Cold ischaemia time, hours	**Mean (SD)**	[redacted]
	Range	[redacted]

SD: standard deviation

The iBox analysis was conducted by the Paris Transplant Group (who developed and own the iBox technique/data) for Hansa. iBox relies on proprietary data that Hansa does not have access to, and so the response that Hansa is able to provide in this regard is, unfortunately, limited. Hansa has contacted the Paris Transplant Group to facilitate the request from the ERG, but have not been able to complete this within the time available for response to these clarification questions.

B6. Please could the company provide generalised gamma and Gompertz extrapolations (including AIC and BIC goodness-of-fit statistics) for all graft-survival and survival with functioning graft data (iBox, all imlifidase and imlifidase unlikely to transplant). In addition, could the company please provide AIC/BIC for the iBox curves currently in the economic model.

The Akaike Information Criterion (AIC)/Bayesian information Criterion (BIC) of the 'all imlifidase' and the 'unlikely to be transplanted' extrapolations are provided in Table B6.1 and Table B6.2 below. Note that in the model, the extrapolations were performed using the WPS software. The Gompertz and the generalised gamma extrapolations were

performed using the R software due to limitation of the WPS software. The WPS software output for the extrapolations of the exponential, log-normal, log-logistic and Weibull presented the logged and unlogged AIC/BIC scores. The model and the company submission (Sections B.3.3.2 and B.3.3.3) presented the logged response scores, but as the R software only reports the unlogged response, Table B6.1 and Table B6.2 below present the AIC/BIC scores of the "unlogged response" for all the different distributions.

Table B6.1 Graft survival extrapolation AIC and BIC scores (unlogged response)

	'All imlifidase' patients		'Unlikely to be transplanted' group	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike Information Criterion; BIC: Bayesian information Criterion

Table B6.2 Patient survival extrapolation AIC and BIC scores (unlogged response)

	'All imlifidase' patients		'Unlikely to be transplanted' group	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC: Akaike Information Criterion; BIC: Bayesian information Criterion

Table B6.3 includes the Gompertz and generalised gamma coefficients, and Table B.6.4 includes the resulting extrapolations.

For the iBox predictions, we are not able to provide AIC/BIC scores because the data were not extrapolated using individual patient data. They were extrapolated based on

the iBox predictions at 10 different time points: Year 1 to Year 10 post-evaluation (with the evaluation performed at 6 months post-graft). In the model, a solver was used for each of the four 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 B6.3 and Table B6.4 also present the iBox Gompertz and generalised gamma extrapolations, along with the sum of least squares.

Table B6.3 Gompertz and generalised gamma coefficients

Function	Parameter	Graft survival			Patient survival	
		iBox	'All imlifidase' patients	'Unlikely to be transplanted' group	'All imlifidase' patients	'Unlikely to be transplanted' group
Gompertz	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Sum of least squares	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Q	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Sum of least squares	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table B6.4 Gompertz and generalised gamma extrapolations

Years	Graft survival						Patient survival			
	iBox		'All imlifidase' patients		'Unlikely to be transplanted' group		'All imlifidase' patients		'Unlikely to be transplanted' group	
	Gompertz	GG	Gompertz	GG	Gompertz	GG	Gompertz	GG	Gompertz	GG
0	[redacted]									
0.5	[redacted]									
1	[redacted]									
1.5	[redacted]									
2	[redacted]									
2.5	[redacted]									
3	[redacted]									
3.5	[redacted]									
4	[redacted]									
4.5	[redacted]									
5	[redacted]									
5.5	[redacted]									
6	[redacted]									
6.5	[redacted]									
7	[redacted]									
7.5	[redacted]									
8	[redacted]									
8.5	[redacted]									
9	[redacted]									
9.5	[redacted]									
10	[redacted]									
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54.5	[redacted]									
55	[redacted]									
55.5	[redacted]									
56	[redacted]									
56.5	[redacted]									
57	[redacted]									

GG: generalised gamma

B7. Could the company comment on the reason for transplantation in their studies, and how this compares to the patients in whom the iBox predictive tool was developed?

The reasons for transplantation within the data utilised for the derivation and iBox are detailed in Table B7.1.

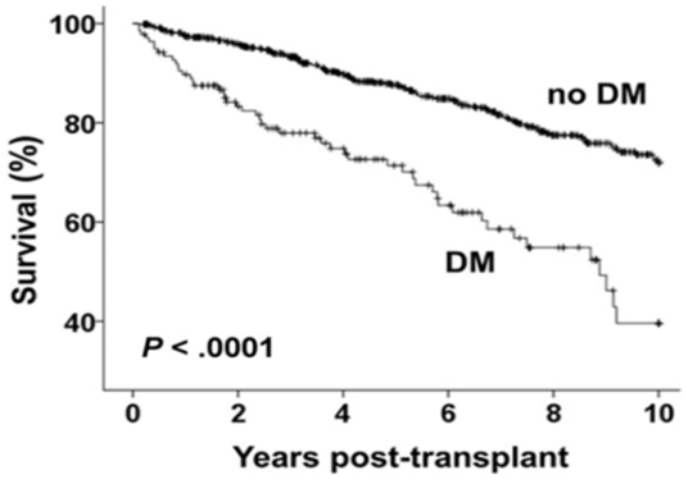
Table B7.1 Causes of transplantation in iBox patients

Cause of ESRD n (%)	Derivation Cohort (n=4000)	European Validation (n=2129)	US Validation (n=1428)	Hansa iBox (n=[redacted])
Glomerulonephritis	1086 (27.2)	584 (27.4)	365 (25.6)	[redacted]
Diabetes	438 (11.0)	316 (14.8)	271 (19.08)	[redacted]
Vascular	296 (7.4)	139 (6.5)	249 (17.4)	[redacted]
Other	2180 (54.5)	1090 (51.2)	543 (38.0)	[redacted]

ESRD: end stage renal disease

It should be noted that the overall iBox cohort contains a higher proportion of diabetes than the imlifidase iBox cohort. Pre-existing comorbidities, such as diabetes, have been shown to have a negative impact on the long term outcomes of kidney transplants. Ten year patient survival rates in patients with diabetes prior to transplant were significantly worse compared to those without the condition (Kleinsteuber et al. Transplant Proc 2018; 50(10): 3232–3241), see Figure B7.1. Therefore, the imlifidase cohort prediction is most likely negatively influenced to some degree by the survival in the large iBox cohort with more diabetes.

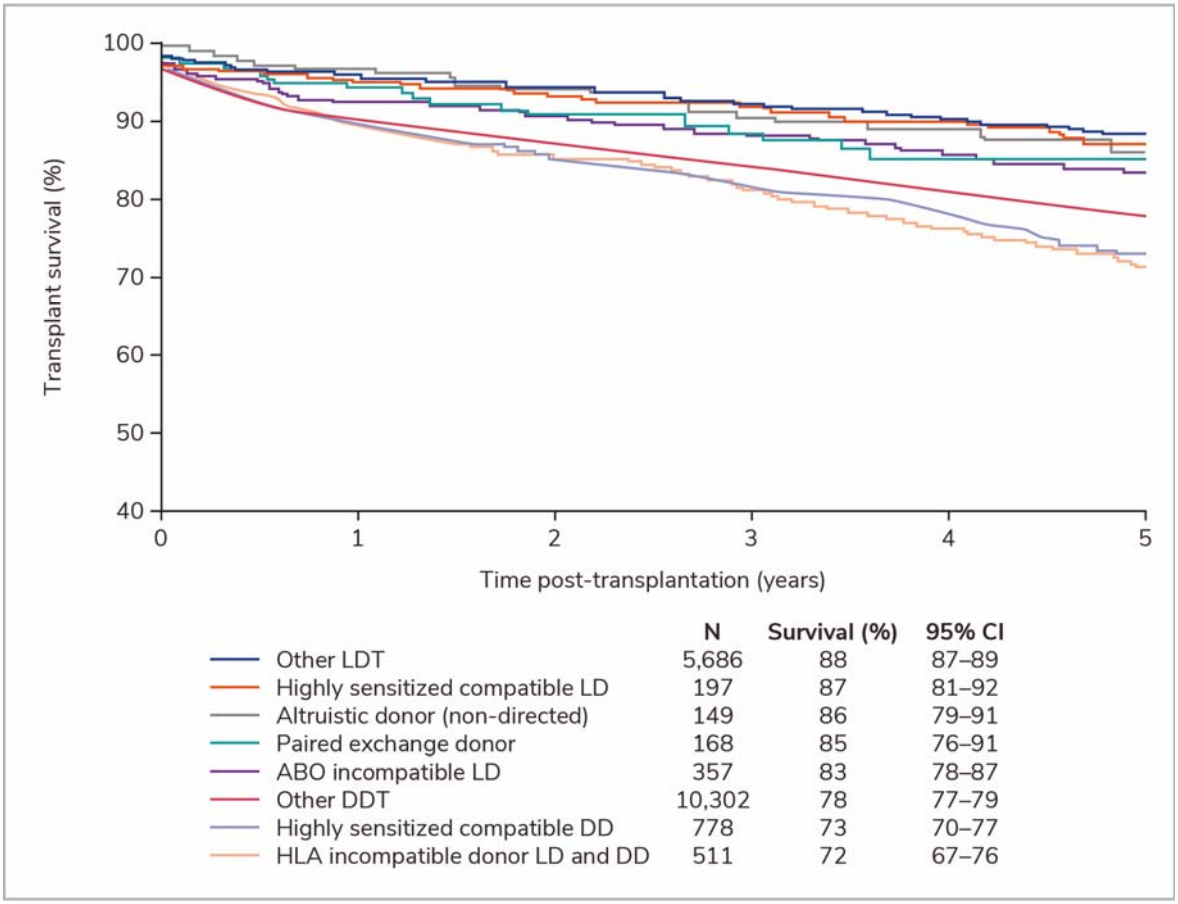
Figure B7.1 Survival of patients with and without diabetes (replicated from Kleinsteuber et al. Transplant Proc 2018; 50(10): 3232–3241)



B8. Are the company able to provide an alternative graft survival estimate from a similar group of patients in the literature? At present the only prediction given is from iBox; alternative estimates would help to reassure the ERG that these are not an aberration.

There are limited literature sources for data in comparable patient populations to those patients that would be administered imlifidase. However, literature values for graft survival are similar to those predicted by iBox for the most similar patient groups for which data are available. The 5 year graft survival rate predicted by iBox was [redacted]%, which is similar to a UK study (Pankhurst et al. Transplant Direct 2017; 3(7): e181), which reported 5 year graft survival rates of 72% for HLA-incompatible transplants and of 73% for highly sensitised compatible deceased donor transplants. These data are reproduced in Figure B8.1.

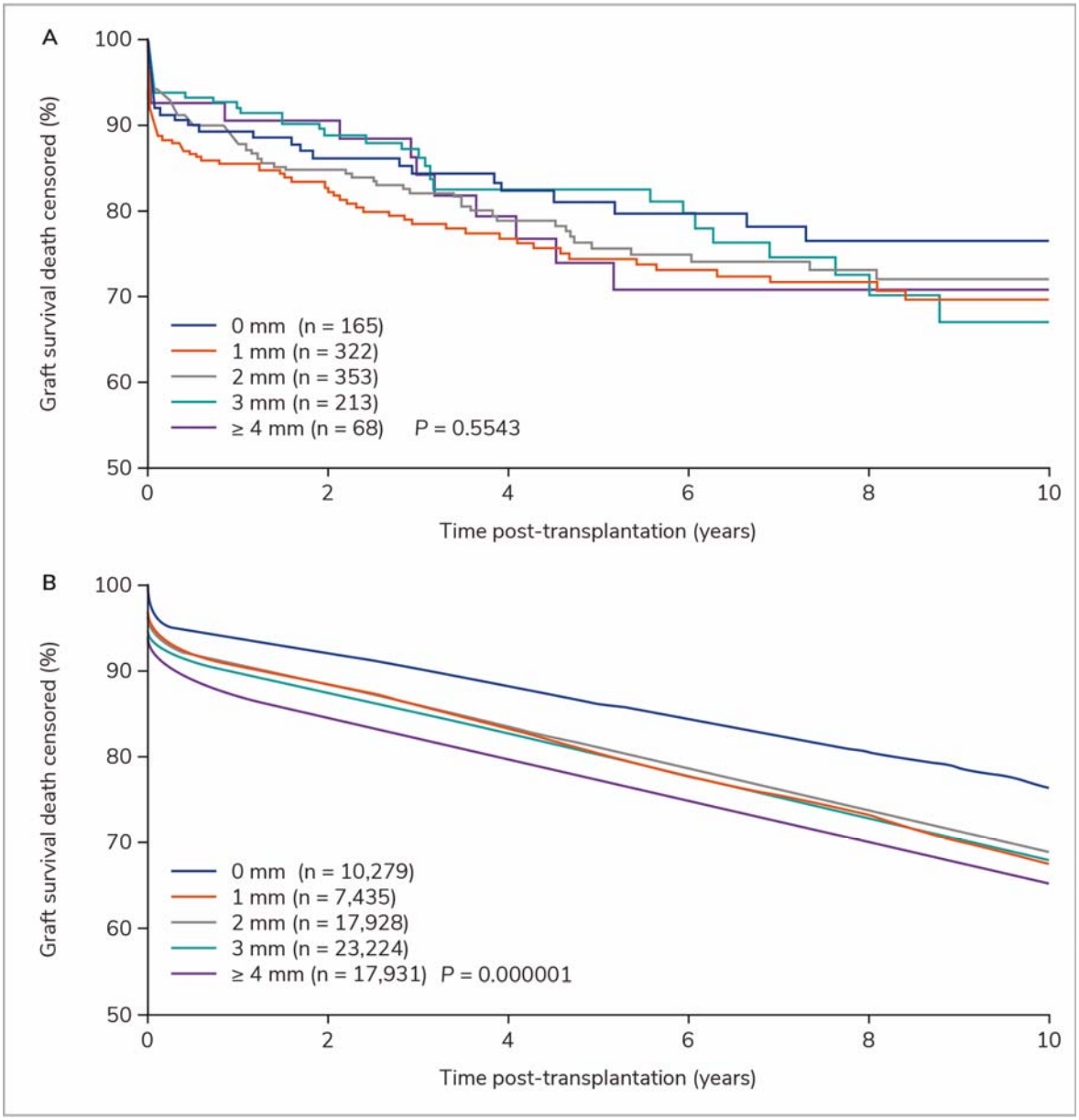
Figure B8.1 Graft survival data reproduced from Pankhurst et al. Transplant Direct 2017; 3(7): e181



CI, confidence interval; DD, deceased donor; DDT, deceased donor transplant; LD, living donor; LDT, living donor transplant

Data from the Eurotransplant Acceptable Mismatch programme is also available that shows graft survival following incompatible transplants (Heidt et al. Transpl Immunol 2015; 33(2): 51–57). The iBox graft survival estimates are similar to those reported for highly sensitised patients with ≥4 mismatches who received transplants (Figure B8.2 A) within and (Figure B8.2 B) outside the Eurotransplant Acceptable Mismatch programme. These literature figures in similar patient groups give confidence in the iBox predicted values. Further reassurance should come from the fact that iBox has been validated (by its producers) in HLA incompatible patients, which are a broadly equivalent patient group to that utilised for this appraisal.

Figure B8.2 Graft survival data reproduced from Heidt et al. Transpl Immunol 2015; 33(2): 51–57



Match effect of HLA antigen mismatches (mm): no effect is seen within the AM program (A; n = 1,121) whereas a match effect can be seen in the Kaplan–Meier analysis for patients receiving a renal transplant outside the AM program (B; n = 76,797). The graphs show 10 year death-censored graft survival data; P value calculated using log rank test.

B9. Please could the company provide a list of the patient ages in those who meet the target population for this appraisal; as age is frequently non-linear in many of the model inputs, it is a required input for many functions.

A histogram displaying patient ages for the 'unlikely to be transplanted' group is presented in Figure B9.1 and shows a relatively normally distributed population around 40–45 years of age.

Figure B9.1 Histogram of patient ages

B10. Please could the company provide an explanation and source for the dialysis survival calculations based on 'ERA-EDTA'. Also if possible, can the company provide marked-up versions of the sources for both 'ERA-EDTA' and 'UKRR'

The UK Renal Registry (UKRR) data initially available in the literature were not considered appropriate for the model as they were only available for the combination of dialysis and kidney transplant (the combination of treatments was defined as renal replacement therapy). In addition, the publicly available information on dialysis survival in the UKRR report only contained survival estimates for two years (compared to 5 years in European Renal Association − European Dialysis and Transplant Association

[ERA-EDTA]). Therefore, the ERA-EDTA dataset was initially considered during production of the model. Subsequently, additional data were requested from the UKRR that would provide the relative risk of death of patients with dialysis compared to the UK general population. The UKRR provided the requested data (see Table 36 of company submission Document B, and the data file supplied to NICE with these clarification responses) and as these data were specific to the UK population, it was determined that they were the best choice and were included in the final model.

Calculation of the survival using the ERA-EDTA:

The dataset from the ERA-EDTA initially considered in the model can be found on Table B.6.6 of the ERA-EDTA Annual Report 2017 (Available at: https://era-edta-reg.org/files/annualreports/pdf/AnnRep2017.pdf).

Table B10.2 below summarises the ERA-EDTA survival information by age group. The columns labelled “Survival (%)” contain the cumulative survival data at 1-, 2-, and 5-years, for incident dialysis patients per age group. The survival percentages were converted into a per-cycle (6 months) probability of death to allow a comparison between survival over time since diagnosis, and across age group. The data show that the probability of death does not vary consistently over time but does vary across age group. As a result, survival based on age group rather than time on dialysis was considered more appropriate and used as an option in the model.

Table B10.2 Dialysis survival by age group (Reproduced from ERA-EDTA Annual Report 2017)

Years	20–44 years		45–64 years		65–74 years		75+ years	
	Survival (%)	Probability of death by cycle (%)	Survival (%)	Probability of death by cycle (%)	Survival (%)	Probability of death by cycle (%)	Survival (%)	Probability of death by cycle (%)
1 year	96.5	1.77	90.4	4.92	82.8	9.01	73.3	14.38
2 year	92.9	1.82	82.8	4.61	70.9	8.24	57.6	12.88
5 year	80.8	2.11	58.8	5.17	41.2	8.49	24.2	13.23

The model assumes that most of the patients will have been on the transplant list for a period of time before receiving a deceased donor kidney. The model cycle probability of death was calculated using the difference between the cumulative survival at 5 years and 2 years. Table B10.3 below summarises the probability of transitioning from dialysis to death that were to be used in the model. An additional issue with the data derived from the ERA-EDTA is that it provides an absolute death transition probability for all causes for dialysis patients, and not a relative risk of death that could be combined with the age-corrected probability of death as derived from the UK Life Tables. This therefore meant that when the ERA-EDTA data were used in the model, there were issues at higher ages where the ERA-EDTA death transition probabilities fell below that for the general population at that age. This was considered counterfactual and led further credence to using the UKRR data within the model.

Table B10.3 Transition probability from dialysis to death

Transition from dialysis to death	Base case
Age: 20–44	2.3
Age: 45–64	5.5
Age: 65–74	8.7
Age: 75+	13.5

B11. Please provide Kaplan-Meier plots of a) graft survival and b) overall survival in the population of interest. Ideally these would include numbers at risk; at present only conditional survival estimates and rates of survival are presented, but the length of follow up is not clear

The Kaplan-Meier graft and patient survival plots are presented in Figures B11.1 and B11.2, alongside with the number of patients at risk for the 'all imlifidase' population.

Figure B11.1 'All imlifidase', graft survival

Figure B11.2 'All imlifidase', patient survival

These data have been derived from the ongoing long-term study of imlifidase (17-HMedIdeS-14) treated transplant patients. As this study is still ongoing only limited data are available, with reducing numbers of patients at longer follow-up times. The drop-off in numbers at risk at 3 years illustrate this, and beyond this time point the data are currently considered unreliable by Hansa as the numbers available for analysis become so limited. The long-term study (17-HMedIdeS-14) aims, when completed, to provide data on 5 years of follow-up post-transplant. The data are presented here for the 'all imlifidase' population, as these data were considered more reliable than those in the 'unlikely to be transplanted' group. This is due to the smaller group size of the 'unlikely to be transplanted' group leading to even smaller patient numbers available at longer follow-up times. The 'unlikely to be transplanted' group was not utilised within the base case analysis of the model and were included as a scenario analysis for the purpose of transparency. Therefore, the 'all imlifidase' data provided above are the most relevant data for consideration in relation to the economic model.

Section C: Textual clarification and additional points

C1. Please provide appendices to all study CSRs

The appendices to all study CSRs have been provided separately to NICE.

NICE National Institute for Health and Care Excellence

Patient organisation submission

ID1672 - Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading charity dedicated to research into kidney disease in the UK. We rely almost wholly on the generous donations of the UK public and we believe that everybody deserves a life free of kidney disease.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have regular contact with people living with CKD as part of our everyday activities as a research organisation. We regularly seek the views and opinions of people living with kidney disease via our Kidney Voices group. This submission is being made from a transcript using the patient's own words. The person interviewed has CKD, high antibodies and has been on the transplant waiting list for over 2.5 years.
Living with the condition	
6. What is it like to live with the condition? What do carers	Diagnosis to dialysis to transplant waiting list

experience when caring for someone with the condition?	I was diagnosed, when my youngest was ten months old, in 2011, I had the biopsy and stuff, it was fine, I was about 40% egfr at the time so I continued to do what I was doing, I was working for an insurer, I'd been with them for 14 years, working part time around school hours, juggling teenagers and three younger ones going to nursery and school. It was probably about 2015 when things were starting to deteriorate, and I was starting to feel it health-wise. I'd been transferred from the low clearance clinic to the Manchester Royal Infirmary (MRI) in Manchester to the renal department there. That's when I wasn't coping well with having to juggle everything, not feeling great and having to face at that stage going to the MRI, to get a plan in place, what treatment would you want in the future, going to all these appointments, going on the transplant list, all that took its toll. I couldn't cope with it anymore, so I went off work with stress, though it was all related, I think I went back at one point, but I couldn't mentally cope with everything, I think I had a bit of a breakdown, but you don't see it at the time because you're trying to cope with what's going on – cope with work, cope with children, all that sort of stuff. So I actually stayed on long term sick and eventually left, which was a hard decision after 14 years, but I'd got to put myself and my family first, so I did that. It took about 18 months where I didn't work at all cos I had to get my head around everything, I started my dialysis and started to feel better… and I looked for a little job to get my hand back in so I'm not just at home feeling sorry for myself. And I'd seen a little advert for a local optician, and they wanted someone three mornings a week, so I did that for almost two years… They knew my situation, when I went for the interview, I explained I didn't know when I'd get a transplant, I had no idea, but they took me on anyway and I was there for two years. That was good, it was something to focus on. Eventually it got to the stage where I wanted to do more hours... so I just started looking, and I was quite nervous, to be honest cos if you've not a proper job interview for financial services in a long, long time, and this job came up an advert for an investment and pension company, I applied … and got the job. It's been a steep learning curve, I wanted something to focus on, rather than sitting and waiting and feeling like everything's on hold.

	I know I may get a transplant from the transplant list, but I think that's very unlikely, I have got very high antibodies. So once I knew that was the thing that geed me along, I was just going to look for something. I'm working part time, 18 hours, plus managing dialysis plus the family.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	I've been on the initial transplant list around 2.5 years. I asked my consultant a question about my antibodies, I'd read lots on the Kidney Research UK site and FB group where people were talking about their antibodies, so I asked my consultant, He said has no one ever spoken to you about it, I said no, He said right, leave it with me .Then I got an appointment to go to the transplant lab to speak with two doctors and they did all these calculations and they give you a print out and it gives you the probability of when you might get a transplant.
8. Is there an unmet need for patients with this condition?	
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Not discussed with the Patient

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Not discussed with the Patient
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	My friend, we met almost 26 years ago when we were first having our children… we lost touch for a few years, then were back in touch. I think it was over a year ago, it's been going on for ages and ages, I'd had a couple of people that had been put forward to be tested – my mum, my husband, my second eldest daughter, two cousins, they weren't matches. People were saying you should just put it on Facebook. I'd always been quite private, but I got to the stage where I thought, do you know what, I should. I posted something, it might have even been something from your website (KRUK), I'd put this is something close to my heart etc. My friend…, she was like, you can have one of mine. It was a bit jokey at first, but then she said no, I'm serious. So, I gave her the details for her to email off. So, she turned out to be a blood match… she had quite a few tests, she had one more to do and an appointment with the doctor before this all happened (lockdown), so it's all been postponed. Last I heard was that her scan to check her kidneys were working, where they put the dye in, was all fine. She needs to have a CT scan… The other family members didn't get past the initial stage, blood type and tissue type…. It's a bit gutting to have all been put on hold, but I've read lots of other people's stories where it's a rollercoaster. So, you try not to get your hopes up, you've just got to try and get on with it, push it to the back of your mind and carry on as best you can really. I've been on the initial transplant list around 2.5 years. I asked my consultant a question about my antibodies, I'd read lots on the Kidney Research UK site and FB group where people were talking about their antibodies, so I asked my consultant, He said has no one ever spoken to you about it, I said no, He said right, leave it with me .Then I got an appointment to go to the transplant lab to speak with two doctors and they did all these calculations and they give you a print out and it gives you the probability of when you might get a transplant. So my antibodies were at 95% which is very high, so there was quite a slim chance, I think after five years on the list it was only a 20% chance of getting a match. So I'm really hoping my friend will be able to go ahead.

	NOTE Since last interviewed, unfortunately a problem has been detected with her friends kidneys and she isn't able to donate after all. The patient is devastated. The patient continues to dialyse at home and is still on the transplant waiting list. She is very conscious that doctors told her, that partly due to her antibodies, after five years on the list she would have a 20% chance of getting a match and has now been on the list for about three years.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Reduced probability of transplant for patients with high antibodies
- Impact on mental health
- Long term impact on quality of life
- Long term impact on economic activity

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS Blood and Transfusion, Organ and Tissue and Donation and Transplantation**

3. Job title or position	**Renal Consultant,** [redacted]
4. Are you (please tick all that apply):	√ an employee or representative of a healthcare professional organisation that represents clinicians? √ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHSBT OTDT are funded by DoH to manage organ and tissue donation in the United Kingdom. Among other responsibilities they ensure the equitable and optimal use of donated kidneys in the UK. A principle which is embodied in the Cadaveric Kidney Allocation Scheme**
4b. Has the organisation received any funding from the manufacturer(s) of the technology in the last 12 months? If so, please state the name of manufacturer, amount, and purpose of funding.	**No**

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To facilitate kidney transplantation of highly sensitised patients who would otherwise be unable to undergo a kidney transplant
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Successful transplantation of a highly sensitised recipient with good long term graft survival (5yrs or more)
8. In your view, is there an unmet need for patients and	Yes, undoubtedly – there are a number of relatively young patients who are destined to remain on dialysis long term as they cannot access transplantation because of pre-formed antibodies

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	By various different methods – Using intelligent delisting techniques, Living donor sharing scheme, HLA incompatible transplantation or by avoiding transplantation and continuing dialysis
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Transplantation Society Guidelines for Antibody Incompatible Transplantation 2015 British Transplantation Society and British Society of Histocompatibility and Immunogenetics guidelines on detection of clinically relevant antibodies
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No – there are various different approaches and numerous studies over the last four decades but there is no gold standard treatment. There are also important and clinically meaningful differences in the way that laboratories measure antibodies. Standardisation of the methods for antibody detection and the definition of unacceptable antigens remains a clinical priority. The UK kidney allocation policy changed in 2019 with the intention of increasing access to transplantation in this population. Preliminary analysis suggests that this initiative has been successful but possibly less so in those patients with CRF = 100%.
• What impact would the technology have on the current pathway of care?	It might permit transplantation in patients who would otherwise be unable to proceed

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No – it would require use in regional or national centres of excellence with standardised definitions of antibody detection and definition. Protocols for treatment of antibody mediated rejection would need to be agreed as well as other standards of care.
• How does healthcare resource use differ between the technology and current care?	The treatment regime is very intensive with significantly intensified immunosuppression (Alemtuzumab, Rituximab, Imlifidase, High dose IvIGs in addition to triple therapy). There must be some concerns over the long-term safety of such regimes and the studies have only relatively short follow up periods. One of the US patients (Lonze et al.) had severe antibody mediated rejection treated with bortezomib, eculizumab and medical splenectomy. This would be very unusual in the UK and would be extremely expensive. There have also been NHSE policy decisions already not to fund bortezomib and eculizumab for this indication.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology would be appropriately used in either a national centre or a limited number of regional centres
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Any centre using it would need to have other technologies available with resources to use them on an urgent basis (e.g. plasma exchange, other high cost drugs and splenectomy)
11. Do you expect the technology to provide clinically	Organ allocation systems inevitably balance the utilitarian need to ensure the best outcome for a limited resource versus the patient-centred approach to achieve the best outcome for any given individual. From a patient-based perspective this technology may enable transplant to proceed where it would otherwise be impossible. However the supply of kidneys for transplantation in the UK is severely limited and any organ used with this technology could be used more effectively and probably much more economically in an

meaningful benefits compared with current care?	alternative recipient. The financial model is patient based and is fundamentally flawed. It would be far more effective to implant cadaveric organs in non-sensitised recipient without the need for this technology. There will always be a cheaper and more effective alternative in the current climate. In addition, the current literature is small and all transplants were carried out in the US and continental Europe. The patient population is heterogenous and the follow up is relatively short. As stated above Herculean efforts were made by the centres to achieve good short-term outcomes which would not be routine practice in any UK centre. These raise significant concerns over long term safety and side effects (infection and neoplasia). A clinical trial in the UK would be more appropriate.
• Do you expect the technology to increase length of life more than current care?	This is unknown as the follow up in the studies is too short
• Do you expect the technology to increase health-related quality of life more than current care?	Again there is insufficient evidence to answer this question. The health economic argument should be based across the healthcare system on the whole though and not simply evaluated from an individual patient's perspective.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It is likely that the technology will be least successful amongst the most highly sensitised patients with the highest antibody levels but this is untested and unanswered by the limited clinical data.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It will be different and new patterns of working with appropriate extra resources will be necessary. This will probably only be possible in a national or several regional centres. At this time it would be inappropriate to invest this money. The question would be best addressed by a UK multicentre study to define the target population and to standardise approaches.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	See above – standardisation would be needed.
15. Do you consider that the use of the technology will result in any substantial health-	No

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes the technology could provide a very significant benefit to selected patients. There remains a need to: 1. Identify the target population 2. Integrate use into the UK allocation policy 3. Standardise H&I practice 4. Protocolise the treatment of antibody recurrence and acute antibody mediated rejction
• Is the technology a 'step-change' in the management of the condition?	It could be if used effectively
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as detailed above

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The long-term effects of this agent are not known as the clinical data has insufficient follow up. There may be direct and indirect effects of the treatment (including effects of the other powerful immunosuppressive agents that may be necessary to ensure successful engraftment)
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No – they use regimes that are not used in the UK
• If not, how could the results be extrapolated to the UK setting?	They cannot – a UK based trial is necessary
• What, in your view, are the most important outcomes, and were they measured in the trials?	Long term graft survival (trials were too short) and quality of life (not measured). That is why a proper trial is required
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	There may be surrogate measures learned from previous experience in HLA incompatible transplantation but these need to be validated with this regime.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of, but long-term safety data will be crucial
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	The clinical data is notable in that is largely single centre in well funded programmes with large resources and with strict adherence to regimes and standardised H&I protocols. Allowing this agent to be freely and widely used in the UK is unlikely to be so successful due to heterogeneity in H&I and treatment protocols as well as availability of resources. Imlifidase should be evaluated in either one or a few centres.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	It is important that the technology is equitably accessed across the UK population

21b. Consider whether these issues are different from issues with current care and why.	They are similar to current issues with geographically variable appetite for risk and access to resources
Topic-specific questions	
22. How long do people with chronic kidney disease who are highly sensitised typically spend on the waiting list for a kidney transplant in England?	For cadaveric donors the mean is 603 days but there is wide geographic variation. The living donors the time is obviously usually shorter. However for this population the time is much longer and some never receive a transplant offer.
23. What proportion of people with chronic kidney disease who are highly sensitised and on the waiting list for a kidney transplant in England, need assistance from a carer?	I don't know but significantly less than half
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Clinical data is limited, short term, in heterogenous subjects and not treated according to existing UK practice
- Health economic modelling must take into account cost to healthcare system as a whole and not be patient centred, especially when the supply of organs in insufficient for the need in the UK
- A UK trial in selected centres of excellence is advised
- Consideration needs to be given to the effects of the new kidney allocation scheme (2019) and how this has affected access to transplantation of this patient group.
- There is no data on quality of life

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Renal Association (UK)**

3. Job title or position	**Consultant Nephrologist and Honorary Clinical Associate Professor**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **yes** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**UK Renal Association is the main professional organisation representing nephrologists and researchers in nephrological disease in the UK. It is funded mainly by annual subscription from members and revenue from the annual congress.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology in the last 12 months? If so, please state the name of manufacturer, amount, and purpose of funding.	**No**

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To enable successful kidney transplant to take place in patients who would otherwise likely have to wait, on average, a lot longer for a suitable deceased donor kidney. By 'successful' I mean that the transplant is associated with duration and quality of life that is better than remaining on the transplant waiting list. This usually means better than the alternative treatment which is dialysis.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A transplant that has similar duration of function and infectious and rejection complications to a standard deceased donor transplantation. Slightly less successful than the outcomes of a standard deceased donor transplant would still be deemed a 'significant treatment response' in this group of patients as this would likely still be deemed better by patients than the alternative of dialysis
8. In your view, is there an unmet need for patients and	Yes.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients are encouraged to find a living kidney donor if possible as this creates the opportunity of either directed donation transplant or transplant via the very successful UK Kidney Sharing Scheme. If that is not available then patients remain on dialysis until a suitable deceased donor is found via the national deceased donor allocation algorithm.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. Renal Association Guideline on Planning, Initiating and Withdrawing Renal Replacement Therapy. https://renal.org/wp-content/uploads/2017/06/planning-initiation-finalf506a031181561659443ff000014d4d8.pdf British Transplantation Society Guidelines for Antibody Incompatible Transplantation. https://bts.org.uk/wp-content/uploads/2016/09/02_BTS_Antibody_Guidelines-1.pdf British Transplantation Society Guidelines for The detection & characterisation of clinically relevant antibodies in allotransplantation https://bts.org.uk/wp-content/uploads/2016/09/06_BTS_BSHI_Antibodies-1.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	My experience is from Scotland but deceased donor retrieval and transplantation is organised at a UK level. The pathway is generally well defined. All centres classify and monitor the circulating HLA antibody profile of patients on the transplant waiting list to identify highly sensitised potential transplant recipients. This profile is reported centrally to NHS Blood and Transplant (NHSBT) and enables determination of what would be unacceptable donor and recipient HLA antibody/antigen mismatches. All deceased donor kidneys in UK are offered nationally to named recipients according to a defined algorithm to balance equity of access and organ utility. This algorithm includes avoiding situations where it is predicted that there will be a positive lymphocyte cross-match in highly sensitised recipients (meaning almost certain early severe,

state if your experience is from outside England.)	irreversible rejection). Within the organ allocation algorithm, prioritisation is given to highly sensitised recipients in recognition of the fact that there are a limited number of suitable kidneys for each of these patients. Despite that, highly sensitised patients still wait longer on average for a deceased donor transplant kidney than patients who are not highly sensitised. There is a grey area in what would be regarded as 'unacceptable' HLA antibody/antigen mismatch between potential donor and recpient. There is variation in the level of risk centres will take with known current or historic circulating donor-specific HLA antibodies or with HLA antigen mismatches from previous transplants. In these circumstances some centres might be willing to recommend and undertake the transplant with enhanced immunomodulation therapy for the recipient, enhanced surveillance for rejection or a combination of both.
• What impact would the technology have on the current pathway of care?	If the technology was successful then it would enable a substantial change to the pathway so that deceased donor organs previously deemed unsuitable for highly sensitised patients could be successfully transplanted
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There is insufficient evidence from clinical trials to know how it will be used. Phase 2 trials suggest some effectiveness in being able to achieve a negative CDC crossmatch ie the transplant can take place with a low chance of of immediate, severe (hyperacute) rejection instead of what would previously have been an unacceptably high chance of hyperacute rejection. But whether this is associated with long transplant survival and acceptable long-term side-effects is not established. If clinical trials establish long-term benefit then it is likely the treatment will be additive to current care.
• How does healthcare resource use differ between the technology and current care?	If the technology is successful then healthcare resource would change for highly sensitised individuals. Instead of requiring dialysis resource they would require transplant resource. In the long-term transplant resource places a lower burden both on the patient and on the health sector.
• In what clinical setting should the technology be used? (For example,	In licensed kidney transplant centres only

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Treatment is by intravenous infusion. There will likely be a need for enhanced monitoring of HLA antibody profiles after transplant and possibly a few more kidney transplant biopsies than before but these will likely not need substantial investment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This remains to be established as published studies are Phase 2 studies of early results after a small number of treated patients have had kidney transplants.
• Do you expect the technology to increase length of life more than current care?	As above
• Do you expect the technology to increase health-related quality of life more than current care?	As above

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Only a treatment for highly sensitised kidney transplant recipients.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will be in addition to current care. The need for concomitant treatments (eg intravenous immunoglobulin, rituximab, prophylactic antimicrobial agents, plasma exchange) remains to be established but is a possibility considering the mode of action of the medicine.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The intended treatment population is clearly defined and the medicine is given as a single infusion protocol at the time of transplant only
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, potentially
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Highly sensitised patients without a suitable living kidney donor face on average a much longer wait for a kidney transplant
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side-effects are not well established from published clinical trials
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The trial in Sweden is more reflective of UK practice than the trial in US though both treatment protocols could be followed in UK.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are: 1. Hyperacute rejection 2. Acute rejection episodes in the first year 3. Infections in the first year 4. Transplant function at 1 year (eGFR) 5. Donor specific antibody profile at 1 year 6. Time to transplant failure Only the first outcome was assessed in clinical trials though 2-6 were assessed at an earlier time-point after transplant.
• If surrogate outcome measures were used, do they adequately predict	No

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The medicine has not been used outwith the reported clinical trials
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	There is no 'real-world' experience of the medicine yet
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No. Equality of access in transplantation is very important but I don't think the availability of this medicine creates any new issues in that respect.

21b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
22. How long do people with chronic kidney disease who are highly sensitised typically spend on the waiting list for a kidney transplant in England?	Median is approximately 5 years compared to 2.5 years for patients who are not highly sensitised. This is based on data from NHS Blood and Transplant presented in 2016. This was used to develop a new allocation algorithm to try to improve access for highly sensitised patients. This algorithm was implemented in 2019 so it is too early to say how much the waiting time has reduced but it will never become the same simply by changing allocation
23. What proportion of people with chronic kidney disease who are highly sensitised and on the waiting list for a kidney transplant in England, need assistance from a carer?	I don't think this information is known. My guess is that it is in the region of 5%
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- This technology shows promise in transplantation for the unmet needs of highly sensitised patients who would benefit from kidney transplantation
- The evidence so far is from small studies of short duration so the true benefit remains uncertain
- If the technology is of long-term benefit then it offers both clinical benefit and potential cost savings as maintenance with a transplant is more cost-effective than maintenance with dialysis
- There are no other equally promising technologies to address the barrier to transplantation for this group of patients.
- Success of this technology needs to be measured in long-term outcomes, not just 'transplant achieved' because there is reason to believe that the benefits might be short-term and so the results of trials with longer term follow up are required.

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Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
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Declared competing interests of the authors	None
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Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
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Copyright	

Author Contributions:	
Caroline Farmer	Project lead, critical appraisal of the company submission, writing and editorial input
Emma Knowles	Critical appraisal of the economic evidence, checked and re-analysed the economic model, carried out further scenario analyses, and drafted economic sections of the report
Fraizer Kiff	Critical appraisal of the clinical background (disease and treatment pathway) and clinical evidence
Linda Long	Critical appraisal of the clinical evidence
Sophie Robinson	Critical appraisal of the literature search strategies and developing and running additional ERG literature searches
Elham Nikram	Critical appraisal of the treatment pathway and economic evidence
Richard Powell	Clinical advice and review of draft report
Jason Moore	Clinical advice and review of draft report
Siân Griffin	Clinical advice and review of draft report
Anthony. J. Hatswell	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report
Louise Crathorne	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report. Guarantor of the report.

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List of key issues

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Abbreviations

Acronym	Definition
Ab	Antibody
AE	adverse event
AMR	antibody-mediated rejection
CDC	complement dependent cytotoxicity
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CIT	cold ischemic time
CKD	chronic kidney disease
CMA	conditional marketing authorisation
CMV	Cytomegalovirus
cRF	calculated reaction frequency
cPRA	calculated panel-reactive antibodies
CS	company submission
CSR	clinical study report
DBD	donation after brain death
DCD	donation after cardiac death
DD	deceased donor
DGF	delayed graft function
DSA	donor specific antibodies
DSU	Decision Support Unit
EBV	Epstein–Barr virus
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European public assessment report
ERA-EDTA	European Renal Association – European Dialysis Transplant Association
ERG	Evidence Review Group
ESKD	end-stage kidney disease
FACS	fluorescence-activated cell sorting
FC	flow cytometry
HCC	half cycle correction
HLA	human leucocyte antigens
HLAi	human leucocyte antigen incompatible

Acronym	Definition
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IgG	Immunoglobulin G
ITT	intention to treat
KDQOL-SF	kidney disease quality of life instrument short form
Kg	kilogram
KOS	kidney offering scheme
LYs	life years
MFI	mean fluorescence intensity
MRU	medical resource use
NHS	National Health Service
NHSBT	National Health Service Blood & Transplant
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	network meta-analysis
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PCC	positive cytotoxic crossmatch
PD	peritoneal dialysis
PhD	pharmacodynamic
PK	pharmacokinetic
PFNC	positive flow, negative cytotoxic crossmatch;
PLNF	positive Luminex, negative flow crossmatch
PRA	panel reactive antibody
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
RCT	randomised controlled trial
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
RRT	renal replacement therapy

Acronym	Definition
SAB	single antigen bead
SAE	serious adverse event
SD	standard deviation
SEs	standard errors
SHELF	Sheffield elicitation framework
SLR	systematic literature review
SmPC	summary of product characteristics
TEAE	treatment emergent adverse event
UKRR	UK renal registry
USA	United States of America
WTP	willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues and the differences in the assumptions of the company and the ERG in economic analysis. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1. Overview of the ERG's key issues

A brief overview of the key issues identified by the ERG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, and 1.5

Broadly speaking, the key issues related to uncertainties about the correct comparator for imlifidase, its potential placement in the treatment pathway, generalisability of the evidence outside of a clinical study (and especially to the UK population), and uncertainty around the effectiveness, safety and impact of imlifidase patients' health-related quality of life (HRQoL).

Table 1: Summary of key issues

ID	Summary of issues	Report sections
Key Issue 1: Relevance of comparators and methodological uncertainty	Relevance of the comparator: should the appraisal consider the costs and benefits of kidney transplant in those not eligible to receive imlifidase	2.4; 3.1 – 3.2; 4.1 – 4.2; 6.2– 6.3
Key Issue 2: Placement of imlifidase in the UK treatment pathway	Placement of imlifidase in the UK treatment pathway: how would the treatment pathway change, and would changes to the Kidney Offering Scheme be necessary	2.3 - 2.4; 3.2.1.3; 3.2.3; 3.2.4.1
Key Issue 3: Generalisability of the evidence to NHS contexts	Generalisability of limited evidence to NHS contexts: assumptions about the outcomes that would occur absent the drug limit generalisability to the UK population	3.1; 3.2.2; 3.6; 4.2.5; 4.2.8; 6.3.6

ID	Summary of issues	Report sections
Key Issue 4: Interpretation of treatment outcomes following transplant	Interpretation of treatment outcomes: lack of comparative data restricts interpretation of the clinical significance of observed effects	3.1; 3.2.1.1; 3.2.2; 3.6
Key Issue 5: Comprehensiveness of the clinical evidence base	Comprehensiveness of the clinical evidence base: significant gaps in the clinical evidence base limit understanding of the efficacy and safety of imlifidase, and its place in the treatment pathway	2.4; 3.2.1.3; 3.2.4; 3.6
Key Issue 6: Comparators in the economic model	Comparators in the economic model: the company's model includes only those patients who were successfully treated with imlifidase, and thus received a transplant	4.2.4; 4.2.6.3; 6.3.2 - 6.5
Key Issue 7: Quality of life data used in the economic model	Quality of life data used in the economic model: no quality of life data were collected for patients who have received imlifidase	4.1; 4.2.5; 4.2.7; 6.5

In the economic analysis, the ERG's preferred assumptions vary from those of the company's in the following ways:

- Using an intention to treat (ITT) population (i.e. including a percentage of patients who do not achieve a negative crossmatch following treatment with imlifidase) [Section 6.2.1]
- Assuming that a proportion of the UK target population would nevertheless receive a transplant without imlifidase [Section 6.2.2]
- Changing the comparator to standard care (i.e. including a proportion of patients in the comparator arm to not receive dialysis) [Section 6.2.3]
- Using more recent and robust utility estimates [Section 6.2.4]
- Using an improved source and distribution of caregiver disutility [Section 6.2.5]
- Reducing the estimated costs for patient transport in the comparator arm [Section 6.2.6]
- Including additional costs for crossmatch and donor specific antibody (DSA) testing [Sections 6.2.7 and 6.2.12]
- Using the average patient weight obtained from the clinical trials to inform dosage [Section 6.2.8].

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by creating a crossmatch conversion and thus allowing patients to undergo transplant. The following are the main benefits of transplant as compared to dialysis in the company model:

- Additional benefits of survival post-transplant
- Reduced cost due to patients no longer requiring dialysis
- Improved quality of life compared to dialysis for patients and caregivers

In order to do this the technology is modelled to affect costs by:

- The one-off costs for treatment with imlifidase followed by the cost of transplantation
- Increasing transplant-related costs, including the costs of long-term effects (e.g. treatment for rejection and graft failure)

The modelling assumptions that have the greatest effect on the ICER are:

- The difference in transplantation rate between imlifidase and standard care. This is both the rate of transplant with imlifidase, and the rate of transplant in the comparator arm
- The treatments received in the comparator arm
- The cost of transplant

1.3. The decision problem: summary of the ERG's key issues

The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal, and identified the following key issues for the committee's consideration.

Key Issue 1: Relevance of comparators and methodological uncertainty

Report sections	**Sections: 2.4; 3.1 – 3.2; 4.1 – 4.2; 6.2– 6.3**
Description of issue and why the ERG has identified it as important	Clinical advice received by the ERG was that imlifidase will not expand the pool of available

	kidneys, but rather equalise access to deceased donor kidneys to include a group that often does not receive them. This suggests that to fully account for costs and benefits, given the scarcity of kidneys (with demand exceeding supply and a waiting list), the appropriate analysis should include the costs and benefits forgone of another patient (who may or may not be highly sensitised) receiving the kidney without the use of imlifidase.
What alternative approach has the ERG suggested?	The ERG has included an illustrative scenario, but made no changes to the base case at this time as the ERG believe the question of scope is for the committee to decide.
What is the expected effect on the cost-effectiveness estimates?	Clinical evidence suggests that graft survival is more durable in patients who are not sensitised as compared to patients who are sensitised, also with lower cold ischaemic time. This improvement in outcomes in conjunction with the elimination of drug cost, leads to imlifidase being dominated with substantial negative net monetary benefit and net health benefit
What additional evidence or analyses might help to resolve this key issue?	To resolve this issue, a decision must be made regarding the appropriate scope for the appraisal, and how this relates to the NICE Guide to the Methods of Technology Appraisal in terms of reference case. This appraisal is unusual in that the decision being made is not on the margin, and in that scarcity of available follow-on treatment (i.e. transplantation) is a limiting factor.

Abbreviations: CIT, cold ischemic time; NICE, National Institute for Health and Care Excellence

Key Issue 2: Placement of imlifidase in the UK treatment pathway

Report sections	**Sections: 2.3 - 2.4; 3.2.1.3; 3.2.3; 3.2.4.1**
Description of issue and why the ERG has identified it as important	The introduction of imlifidase would alter the likelihood of transplant for highly sensitised patients, it is unclear how this would change the positioning of these patients in the Kidney Offering Scheme (KOS). Changes to the KOS may be required to account for imlifidase. It is also unclear when imlifidase would be used in the process, and the impact that this will have on testing and the timing of transplant. Clinical advice to the ERG suggests that imlifidase would be administered after evaluation of the retrieved kidney – potentially increasing cold ischaemic time (CIT). There is a further lack of clarity around the time required for imlifidase to act before a crossmatch test can be conducted to confirm

	whether treatment has been successful and a transplant can go ahead. As clinical advice to the ERG was that the results of a crossmatch test may then take several hours to receive, there is outstanding uncertainty about the effect of this may have on CIT. Finally, there is uncertainty about the timing and frequency of donor specific antibody (DSA) testing following transplant.
What alternative approach has the ERG suggested?	Without further consultation it is not possible to ascertain the changes to the KOS which may be required in response to the introduction of imlifidase. A comparison of the UK transplant protocol to those used in the clinical trial countries may elucidate the specific pathway which is likely to be utilised in the UK. Further knowledge of this process would also allow more comprehensive consideration of other factors such as the CIT.
What is the expected effect on the cost-effectiveness estimates?	It is difficult to say how the KOS would affect the cost effectiveness of imlifidase without further information. The ERG acknowledges the possibility that the treatment pathway in the UK could be problematic. For example, increased CIT compared to current transplant procedures may lead to poorer outcomes. Conversely earlier use of imlifidase (prior to kidney assessment) would lead to increased costs, and given a patient may only receive imlifidase once, may prevent the patient receiving a transplant should the kidney prove unfit for transplant. Either of these issues would increase the incremental cost-effectiveness ratio (ICER) and thus necessitate a protocol for appropriate use
What additional evidence or analyses might help to resolve this key issue?	It may be necessary to consult policy makers to establish how they would anticipate altering the KOS in response to the introduction of imlifidase. A more in-depth description of the positioning of imlifidase, in the context of the protocols used in the trial countries, would allow further analysis of the effect on CIT and other treatment pathway-related factors.

Abbreviations: CIT, cold ischemic time; DSA, donor specific antibodies; ERG, Evidence Review Group; KOS, kidney offering scheme

1.4. The clinical effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the clinical effectiveness and safety evidence presented in the CS, and identified the following key issues for consideration by the committee.

Key Issue 3: Generalisability of the evidence to NHS contexts

Report sections	Sections: 3.1; 3.2.2; 3.6; 4.2.5; 4.2.8; 6.3.6
Description of issue and why the ERG has identified it as important	The clinical evidence presented consists solely of 4 single-arm studies, comprised of a total of 54 patients (25 of whom were considered to be most consistent with the decision problem population). None of the studies were conducted in the UK, and the ERG understands that national and local protocols for kidney transplantation have considerable impact on the treatment pathway. The studies were all early phase trials, and involved variation in trial protocols, as understanding of imlifidase developed. Finally, the definition of the target population as specified in the conditional marketing authorisation for imlifidase is a new indication in this population. While appropriate, there is no published data for the demographics and outcomes of this group as would be seen in NHS contexts without the use of imlifidase. Several outcomes included could also have been subject to bias from confounding and distribution of effect modifiers. As relative treatment effects cannot be estimated from the trials, the company's assertion of effectiveness relies on an implicit assumption that absent the drug, specific outcomes (such as negative crossmatch tests) would not have been observed. The ERG regards that these issues complicate considerably the ability to generalise effects to the UK population, especially given that the company's economic model relies in its base case on this implicit assumption.
What alternative approach has the ERG suggested?	The ERG acknowledges that, as is also acknowledged below, a form of matched comparison would have increased confidence in the analysis.
What is the expected effect on the cost-effectiveness estimates?	The ERG cannot quantify the impact on the ICER of a lack of generalisability.
What additional evidence or analyses might help to resolve this key issue?	A matched analysis with patients receiving dialysis while on the waiting list for a transplant would greatly augment the evidence base for imlifidase and improve confidence in longer-term outcomes.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio

Key Issue 4: Interpretation of treatment outcomes following transplant

Report sections	Sections 3.1; 3.2.1.1; 3.2.2; 3.6
Description of issue and why the ERG has identified it as important	The ERG accept that it was not possible to conduct an RCT to evaluate imlifidase in this population; however, the ERG considered that the lack of matched evidence represents a limitation in the evidence base. In the absence of more rigorous, matched data, the company did not present a systematically identified evidence base from which to make naïve comparisons with trial outcomes. While these comparisons would have limitations, they nevertheless would have aided interpretation of the magnitude of clinical effect data (for example, whether the rate of rejection following transplant is comparable with non-sensitised deceased donor transplants).
What alternative approach has the ERG suggested?	Within the timescale it was not possible for the ERG to conduct a systematic review of transplant outcomes in comparable populations; however, where possible the ERG did conduct hand searches to identify supplementary sources of evidence to inform the interpretation of clinical data. The interpretation of transplant outcomes remains uncertain.
What is the expected effect on the cost-effectiveness estimates?	Transplant outcomes following imlifidase are based on those reported in the included trials, and extrapolated using iBox. It is not clear whether the studies conducted by the company are in a more- or less-favourable population, and therefore the validity of the clinical data used in the model is unclear. Without further evidence, the potential impact of this issue on the ICER is unclear.
What additional evidence or analyses might help to resolve this key issue?	As above, a matched analysis with patients receiving dialysis while on the waiting list for a transplant would augment the evidence base for imlifidase and improve confidence in longer-term outcomes. In the absence of this, greater confidence could be drawn from the presentation of a larger evidence base demonstrating outcomes in a comparable population, and ideally identified systematically from the literature.

Abbreviations: ERG, Evidence Review Group; RCT, randomised controlled trial

Key Issue 5: Comprehensiveness of the clinical evidence base

Report sections	Sections: 2.4; 3.2.1.3; 3.2.4; 3.6
Description of issue and why the ERG has identified it as important	The ERG considered that the evidence reported in the CS from the company's clinical evidence review was poorly reported and contained

	significant gaps that limited understanding of the clinical and safety outcomes following treatment with imlifidase. Not all outcomes were evaluated in each trial; however, where outcomes were evaluated these were not always reported (for individual trials as well as for the pooled analyses conducted by the company). Moreover, where outcomes were reported, the timing of measurement was often unclear, and continuous data were frequently reported without variance data. This creates significant uncertainty about the efficacy and safety of imlifidase in the target population. In particular, the ERG was concerned that poor reporting of crossmatch conversion data (the primary outcome for the clinical trials) and the type and consequences of AMR episodes.
What alternative approach has the ERG suggested?	The ERG has drawn conclusions on the basis of the evidence available, though uncertainties remain. It would be help to reduce uncertainty in the evidence, and promote understanding, if the company could provide further evidence during technical engagement.
What is the expected effect on the cost-effectiveness estimates?	This issue is not expected to influence the cost-effectiveness estimates presented by the company.
What additional evidence or analyses might help to resolve this key issue?	The ERG would like to see all scoped outcomes that were measured in the trials reported for all the included studies and the relevant pooled analyses. Outcome data should follow gold standards for the reporting of clinical and safety evidence in a NICE submission; including specifying the timing and measurement of outcomes, variance data for continuous outcomes, and numerator, denominator, and percentage data for dichotomous outcomes. In addition, thresholds used to categorise continuous outcome data should be used consistently across studies, and ideally supported by literature.

Abbreviations: ERG, Evidence Review Group; RCT, randomised controlled trial

1.5. The cost effectiveness evidence: summary of the ERG's key issues

Key Issue 6: Comparators in the economic model

Report sections	**Sections: 4.2.4; 4.2.6.3; 6.3.2 - 6.5**
Description of issue and why the ERG has identified it as important	The company model used a post-hoc scope i.e. *given* a patient got a transplant, versus *remaining on dialysis*. This does not match the NICE scope, which compares imlifidase versus clinical management without imlifidase. In reality not all patients who receive imlifidase are able to receive a transplant, and not all patients

	who are untreated with imlifidase are necessarily on dialysis or fail to receive a transplant – particularly in light of the revised KOS, where greater priority is given to highly sensitised patients.
What alternative approach has the ERG suggested?	The ERG has effectively implemented an 'Intention To Treat' analysis, accounting for not all patients (circa 96%) on imlifidase receiving transplant, and highly sensitised patients receiving dialysis and transplants using data provided by NHS Blood and Transplant (NHSBT) from this specific patient group.
What is the expected effect on the cost-effectiveness estimates?	There is a marked increase in the ICER as the rate of transplant moves from 100% vs 0%, to 96% vs 31% and the use of dialysis for non-transplanted patients falls from 100% to 85%
What additional evidence or analyses might help to resolve this key issue?	Following a request from the ERG, data was provided by NHS Blood and Transplant on a group of very highly sensitised patients which reduces the uncertainty around this aspect. There does exist however uncertainty about the rate of transplant going forward, and the length of time which patients could remain dialysis free. Moreover, it is likely that an alternative model structure would have better accounted for complexity of the treatment pathway.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio

Key Issue 7: Quality of life data used in the economic model

Report sections	**Sections: 4.1; 4.2.5; 4.2.7; 6.5**
Description of issue and why the ERG has identified it as important	No quality of life data were collected in the company studies, with literature data from pre-2005 used in the economic model which has methodological issues
What alternative approach has the ERG suggested?	The ERG performed a literature search, which identified a systematic review of utility values published after the CS (Cooper et al. 2020[44]). The ERG considered that this source was a more relevant reference; however, uncertainty on the impact of imlifidase on quality of life remained uncertain.
What is the expected effect on the cost-effectiveness estimates?	There was an increase in the ICER using the revised data, but structural uncertainty remained as to whether these values were appropriate
What additional evidence or analyses might help to resolve this key issue?	Data collection using Patient Reported Outcomes from patients who have received imlifidase and undergone a transplant.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio

1.6. Other key issues: summary of the ERG's views

No other key issues were identified.

1.7. Summary of ERG's preferred assumptions and resulting ICER

A summary of ERG's preferred assumptions and resulting ICER is provided in Table 2. Changes to the ICERs in the ERG base case related primarily to Key Issue 6; additional changes are described and justified in Section 6. Modelling errors identified and corrected by the ERG are described in Section 5.2. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.

Table 2: Summary of ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER	ICER (change from company base case
Company base case (deterministic)	[redacted]	[redacted]	£30,641	-
Company base case (probabilistic)	[redacted]	[redacted]	£31,948	-
ERG error fixes				
Apply 0-6 month transplant maintenance costs	[redacted]	[redacted]	£31,953	£1,311**
Apply imlifidase and transplant AE's to all imlifidase	[redacted]	[redacted]	£30,683	£42**
Apply caregiver disutility to Li *et al.* (2017)*	[redacted]	[redacted]	£30,641	£0**
Apply AE Cycle 5+ costs to transplant AEs	[redacted]	[redacted]	£30,618	-£23**
Company corrected base case (deterministic)	[redacted]	[redacted]	**£31,971**	**£1,330****
Company corrected base case (probabilistic)	[redacted]	[redacted]	**£33,563**	**£1,615****
Company corrected base case used as start point for ERG analyses, below				
Reduce the proportion of imlifidase patients to receive transplant – 96.3% (see Key Issue 6)	[redacted]	[redacted]	£34,459	£2,488***
Allow a proportion of dialysis patients to receive a transplant – 31.44% (see Key Issue 6)	[redacted]	[redacted]	£59,335	£27,364***

Scenario	Incremental cost	Incremental QALYs	ICER	ICER (change from company base case
Apply NHSBT proportion of dialysis modality, including not on dialysis (see Key Issue 6)	[redacted]	[redacted]	£40,999	£9,028***
Utility source – Cooper *et al.* (2020)	[redacted]	[redacted]	£38,672	£6,701***
Caregiver disutility source – Thomas *et al.* (2015)	[redacted]	[redacted]	£31,431	-£541***
Reduce the proportion of HD patients with a caregiver to 90%	[redacted]	[redacted]	£32,009	£38***
Redistribute hospital-paid dialysis travel cost (see Key Issue 6)	[redacted]	[redacted]	£37,085	£5,114***
Apply crossmatch test cost per imlifidase dose	[redacted]	[redacted]	£32,049	£78***
Change average patient weight to 69 kg	[redacted]	[redacted]	£31,942	-£29***
Include DSA test costs	[redacted]	[redacted]	£32,344	£373***
ERG base case (deterministic)	[redacted]	[redacted]	**£95,131**	**£63,160*** **
ERG base case (probabilistic)	[redacted]	[redacted]	**£97,728**	**–**

Abbreviations: AE, Adverse event; DSA, donor-specific antibodies; ERG, Evidence Review Group; HD, haemodialysis; HR, Hazard Ratio; ICER, incremental cost-effectiveness ratio; kg, kilogram; NHSBT, National Health Service Blood and Transplant; QALY, quality-adjusted life year; vs, versus

Notes:

* The base case analysis does not use the Li et al. (2017) utility values, hence no difference is observed in the base case ICER when including this correction.

** Deterministic = company corrected base case (deterministic) vs company base case (deterministic), £30,641; Probabilistic = company corrected base case (probabilistic) vs company base case (probabilistic), £31,948

*** Change versus company corrected base case £31,971

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

End stage kidney disease (ESKD) is the last of five stages of chronic kidney disease (CKD) defined as an estimated glomerular filtration rate (eGFR) below 15mL/min/1.73m^3 or dialysis dependency. Significant contributory factors to ESKD in the UK are diabetes, glomerulonephritis and high blood pressure[1,2]. Around 3.6 million people over the age of 16 years in the UK suffer from CKD in Stages 3-5. Prevalence is higher in older people and women[3]. In 2019/20 there were 2,283 kidney transplants, from deceased donors, carried out.[4] While waiting for a transplant, patients are treated with dialysis, although prolonged dialysis (>1 year) is associated with inferior outcome following transplantation.[5] Dialysis also has a considerable impact on the lives of patients with ESKD, and their family and carers. The median waiting time for those transplanted between 1st April 2018 and 31st March 2019 was 1,088 days.[6] The wait for a kidney is due to the need to find an appropriate donor match, but also due to the deficit in the number of kidneys available for transplant: in 2019, there were 4,647 patients on the waiting list for a kidney in the UK[6].

In the UK, deceased donor kidney transplants are coordinated by NHS Blood and Transplant (NHSBT) via the Kidney Offering Scheme (KOS) through which a specific recipient is identified for a given donor. When a kidney becomes available, an algorithm is used to identify the most appropriate recipient, considering their blood group, waiting time, Human Leucocyte Antigen (HLA) compatibility and a number of other factors[7]. It is also possible, though unlikely, that patients will receive a living donor transplant, such as coordinated via the Kidney Sharing Scheme. However, imlifidase is not indicated for living donors and, as such, they are not relevant to this appraisal.

There are two aspects to HLA compatibility. The first is the similarity of HLA types between the donor and recipient. The second is whether the recipient has any preformed HLA antibodies, stimulated following prior exposure to non-self HLA by pregnancy, blood transfusion, or previous transplant. If a transplant is performed in the presence of donor specific HLA antibodies (DSA), these can cause rejection, and if present at a significant level are considered an absolute veto to transplantation. While desensitisation therapies can be considered to mitigate the risk of antibody mediated rejection (AMR), the risks associated with the required immunosuppressive regimen must be weighed against the benefits of transplant on an individual basis. The range of antibodies can be defined by the Luminex assay, and their clinical significance assessed by

crossmatch tests between the donor lymphocytes and recipient serum (by flow cytometry [FACS] or cytotoxicity assay [CDC]). Although the production of HLA antibodies may have been in response to limited specificities, these are often cross reactive with other HLA types. A patient with HLA antibodies is referred to as “sensitised”. The degree of sensitisation is expressed as the calculated reaction frequency (cRF), which is the percentage of the blood group identical population against whom the recipient has detectable antibodies. A highly sensitised patient is one with a cRF >85%. It is harder to identify a compatible recipient for this group (who make up 26% of the current waiting list[8]). In recognition of their potential for longer waiting time, the KOS includes prioritisation for sensitised patients, including absolute priority for those with a cRF of 100%, matchability score 10 (the decile of recipients predicted to have the longest waiting time) or waiting time of at least seven years. In the last five years, 12.8% (n=1439) and 3.8% (n=425) of deceased donor transplants were performed in patients with a cRF of ≥85% and ≥99%, respectively (NHSBT data[9]).

The majority of recipients receive a transplant from a blood group and HLA compatible donor. However, given the potentially long waiting time of sensitised patients, with accrual of dialysis-related morbidity and mortality, there has been intense interest in the use of desensitisation regimens to lower HLA antibodies, prevent rebound in levels and permit transplantation. This more feasible for living donor transplants, where the time frame of antibody removal is defined. Although the outcomes following HLA incompatible (HLAi) transplants (i.e. those performed following antibody removal) are inferior to compatible transplants, this may be preferable to the expected prolonged dialysis for selected and appropriately counselled recipients. Currently, HLAi deceased donor transplantation is performed rarely, as there is insufficient time to lower antibody levels sufficiently to permit transplantation.

The company have presented evidence for the effectiveness of imlifidase for facilitating deceased donor kidney transplants in highly sensitised patients, who have a very high cRF (>95%) and who are unlikely to receive a transplant under the current UK KOS. The Evidence Review Group (ERG) believe that the Company Submission (CS) provides an acceptable description of the condition; its pathophysiology, natural course and epidemiology; and a reasonable description of the current standard of care – though these issues are not fully reflected in the economic model, which forms the substance of the ERG’s additional work.

2.2. Background

Imlifidase (IdeS, Idefirix™) is an extracellular cysteine proteinase enzyme produced by streptococcus -pyogenes.[1,3,10,11] It works by cleaving IgG into F(ab')2 and Fc fragments, thus inactivating the patients' antibodies against donor antigens (donor specific antibodies [DSAs]). The company therefore suggest that the rapid action of imlifidase reduces anti-HLA antibodies sufficiently to allow transplants from deceased donors where patients have a positive crossmatch. Imlifidase has a conditional marketing authorisation[12] to treat those unlikely to receive a transplant under the existing protocols of the KOS. This is defined by the company as those with a cRF over 95% with a positive crossmatch test to an available donor. Where these patients are not matched through the kidney offering scheme (KOS) and there is no compatible living donor available, there are currently no alternative treatment options occupying this position, meaning that if imlifidase were effective, it could open up the possibility of transplant from a deceased donor in a population where this would not previously have been possible. This would increase the portion of the donor pool from which these highly sensitised patients are able to receive a kidney. The ERG considered the proposed positioning of imlifidase to be appropriate despite there being no agreed clinical definition of the population who would be 'unlikely to receive transplant'. Clinical advice to the ERG was that this group is recognisable, and that the targeting of imlifidase meets the greatest need. The ERG acknowledges that some clinician discretion is necessary and appropriate, though also that these patients are (agreed by all) to be 'unlikely' to receive a transplant, and not 'unable' to receive a transplant (Key Issue 6).

2.3. Current treatment pathway

The proposed treatment pathway for imlifidase leaves some uncertainty around specific treatment protocols. Initially, once a patient has Stage 5 CKD (an eGFR ≤15), a decision may be made to add them to the transplant waiting list. When added to the transplant waiting list, patients are assessed for the presence of anti-HLA antibodies and their cRF determined. Although pre-emptive transplantation is desirable due to improved patient outcomes, many patients require dialysis while waiting for a transplant to become available. A proportion of highly sensitised patients do not receive dialysis (22.1% of patients with cRF ≥85% on the waiting list[9]). The ERG noted that this was not captured in the company's representation of the treatment pathway and in their economic model (see Key Issue 5).

When a deceased donor kidney becomes available, it will be allocated to a recipient through the KOS. This system considers many factors in order to account for the urgency of the transplant

and the suitability of potential recipients. The algorithm used by the KOS to allocate kidneys was altered in 2019 to give greater priority to sensitised patients. As this change was made recently, and because of the impact of the backlog of highly sensitised patients that have accrued on the waiting list, in addition to the impact of COVID-19 on transplant rates, the impact of this change on the rate of transplant is not yet certain. However, similar changes in other countries have shown reductions in waiting times for highly sensitised patients[13]. It is not known whether it would be appropriate to adjust the KOS algorithm to ensure equality of access if imlifidase were to be introduced. The company provided no comment on this, however the ERG considered it possible that if treatment with imlifidase increases the donor pool for those patients with cRF >95%, and these patients continue to be prioritised with the changes to the KOS algorithm introduced in 2019, then patients not within this group may be disadvantaged by comparison. Clinical advice to the ERG on this was conflicting, and this remains an outstanding area of uncertainty. The ERG considered that further input from stakeholders could help to resolve this issue.

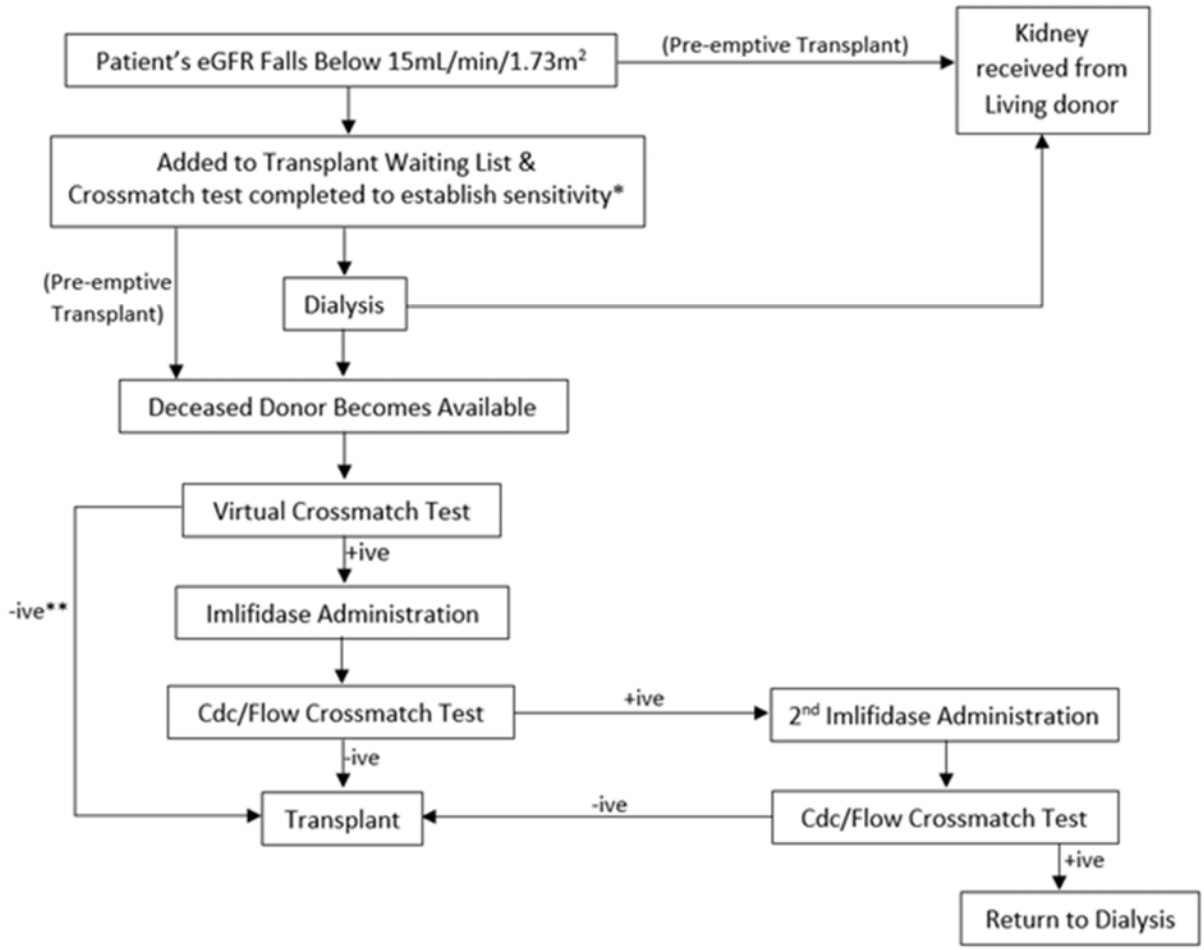
Based on the information provided in the CS, there also remains uncertainty around the timings of organ retrieval and the administration of imlifidase in the treatment pathway. Noting that a crossmatch test is need to determine whether imlifidase has been successful before a transplant can occur, the ERG considered it possible that, once a potential donor match has been identified, the kidney is retrieved from the donor to ensure that it is suitable before imlifidase infusion begins. A crossmatch test will then be required to ensure crossmatch conversion. Clinical advice to the ERG suggests this is the most likely treatment pathway to be used in practice, although it may cause an increase in cold ischemic time (CIT) while treatment with imlifidase and subsequent crossmatch testing is completed prior to transplant.

Due to the known detrimental impacts of long CIT on transplant outcomes, the target for CIT in the UK is <12 and <18 hours for donation after cardiac death (DCD) and donation after brain death (DBD), respectively. CIT of 24 hours maximum was strongly advised by the ERG's clinical advisors. From the available data, it appears that imlifidase may act quickly for many patients, though the data was not available to conclude on an average rate of response, and there was wide variation between patients. In one of the included trials, the reduction in median DSA levels reached their lowest between a range of [redacted] after treatment (pg. 73 of CS Doc B). Further guidance from the company is needed to determine at what time point following imlifidase infusion a crossmatch test should be carried out in practice to identify a crossmatch, and to what extent this is expected to impact on the kidney CIT. Moreover, the ERG

understands that it may take four to six hours to receive the results of a crossmatch test (time depending on local protocols), which may need to be doubled in the event that a second test is required (as in [redacted] of patients in the clinical trials). The ERG was also concerned that this process may inflate the kidney CIT, which was supported by the high mean CIT evident in the company's trials of imlifidase (in the decision problem cohort, mean CIT was [redacted] hours; CS Doc B, p.82). Any additional time accrued to CIT by the above processes may be even more relevant in the context of the NHS, where CIT is already 12 and 13 hours for DCD and DBD respectively[6]. Clinical advice suggested that where additional time is taken, it would not be wasted since other preparation can be done in the interim, however, where these processes exceed the average CIT seen in the NHS at present, the ERG does not see how the excess time can be utilised. Clinical advice also suggested the possibility that imlifidase could be administered at the time of organ retrieval if the HLA type is known, in order to minimise additional CIT. Overall, the ERG considered that the timing of imlifidase treatment and subsequent crossmatch testing needs further clarification, as well as the potential impact that implementation may have for the CIT and for patient outcomes following transplant.

Another area of uncertainty is in the requirement of donor-specific antibody (DSA) tests following transplant in highly sensitised patients. DSA testing is routinely conducted after transplant to detect for signs that DSA specific antigens have rebound, and indicate a risk of rejection. DSA testing is utilised on an individualised basis and the frequency of testing varies by centre. At clarification [question A16], the company stated that they expect that the rate of DSA testing should be consistent with existing guidelines for patients who have undergone de-sensitisation prior to transplant (BTS guidelines[14]). These guidelines allow for a routine test of at least once in the first 12-months following transplant, in addition to testing in response to signs that antibodies may have rebounded. However, the company acknowledge the lack of data available for this population, and data reported in the CS for the included clinical trials of imlifidase was not sufficient to estimate the approximate frequency of testing that would be required. Clinical advice received by the ERG suggests that more frequent DSA testing may be required and that this may incur additional costs. However, clinicians stated that this was an assumption until further experience or research with imlifidase treatment in this population is available.

Figure 1: Proposed treatment pathway for highly sensitised ESKD patients in the UK



Abbreviations: eGFR, estimated glomerular filtration rate; Cdc, complement dependent cytotoxicity

Notes: * Multiple crossmatch tests may be required if on waiting list for an extended period since sensitivity can be increased by events such as pregnancy or transfusion (although clinicians aim to reduce the likelihood of an increase in sensitivity where possible). ** Clinical opinion is that it is unclear whether a virtual crossmatch would be sufficient in this scenario. It is possible that a crossmatch test would be required irrespective of the outcome of the virtual crossmatch.

2.4. Critique of company's definition of decision problem

The ERG's critique of the company's definition of the decision problem is provided in Table 3. Despite the lack of a clear definition around the criteria for patients to be defined as 'unlikely to receive a transplant' under existing systems, the ERG considered this definition of the population to be appropriate: clinical advice to the ERG was that these patients are known to clinicians, and are also those with the greatest need. However, the ERG considered that the

lack of a clear definition for these patients nevertheless causes some uncertainty about the typical treatment pathway and outcome for these patients. A key discrepancy leading from this is a disagreement between the company and the ERG about the scoped comparator for imlifidase: the company state that no patients in the 'unlikely to be transplanted' population will receive a transplant in their lifetime, while the ERG considered the definition to allow a 'non-zero' possibility of transplant. To this point, the ERG requested additional data from NHSBT[9], which showed that as of September 2020, 15.6% of very highly sensitised (cRF ≥99%) patients on the waitlist were not receiving dialysis. This issue is discussed in further detail in the cost-effectiveness chapter (see Section 6.3.3).

The conditional marketing authorisation (CMA) for imlifidase states that patients are highly sensitised 'unlikely to receive a transplant' through existing systems. However, at clarification [A8], the company propose that a minority of patients that may receive imlifidase fall outside the 'unlikely to be transplanted' group as defined by the company; namely with cRF ≥95%. These patients were defined as patients with a sensitisation in the range 85–95% but have a particular immunological profile that makes them unlikely to receive a transplant (e.g. high total mean fluorescence intensity (MFI) load and/or a number of problematic DSAs. These patients were not included in the pooled analysis of the decision problem cohort conducted by the company for this submission, and prioritised by the ERG in their appraisal. The ERG considered this population to be beyond the scope of this appraisal as it was unevidenced by the company in the presented analyses.

Relatedly, the ERG considered that the scope for this appraisal excluded consideration of the potential impact of imlifidase on the broader KOS, with respect to the way in which the re-distribution of kidneys from within a finite donor pool would impact on patients outside of the licensed indication. Full consideration of this alternative view of the decision problem was not feasible within the timeframe of this appraisal, however the potential impact of incorporating the opportunity cost of donor kidneys is explored by the ERG in Section 6.3.11

The ERG also noted the gaps in the evidence base according to the scoped outcomes. Otherwise, the ERG was satisfied with the remit of the CS in respect to the decision problem.

Table 3: Summary of decision problem

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with chronic kidney disease awaiting a kidney transplant from a donor, who are highly sensitised with HLA and have a positive crossmatch with the donor.	Adults with chronic kidney disease awaiting a kidney transplant from a deceased donor, who are highly sensitised with HLA, have a positive crossmatch with the donor and are unlikely to be transplanted under the kidney offering scheme.	Decision problem is more restricted due to the approved indication for imlifidase.	The ERG noted the restricted population and on the basis of clinical advice agreed that this was reasonable, though noted that this increased some methodological uncertainties in the appraisal.
Intervention	Imlifidase in addition to an immunosuppressive regimen.	As per the scope.	N/A	N/A
Comparator(s)	• Kidney transplant (may include plasma exchange) • Haemodialysis/ haemodiafiltration or peritoneal dialysis	Established clinical management without imlifidase: • Haemodialysis/ haemodiafiltration or peritoneal dialysis	Dialysis is the only alternative treatment option available to the population of interest, as they are defined as being unlikely to be transplanted due to their sensitisation and have a positive crossmatch that is a contraindication to transplant	The ERG regarded that the comparator in this case could have been better understood as clinical management without imlifidase, due to some probability of transplant absent imlifidase and a percentage of patients on the transplant waiting list who are not receiving dialysis for a period of time.
Outcomes	• Crossmatch conversion efficacy (ability to create a negative crossmatch test in people who exhibit donor specific antibodies) • Mortality • Kidney function (eGFR) • Time to graft failure • Time to rejection; type of rejection; number of rejection episodes	• Crossmatch conversion efficacy (ability to create a negative crossmatch test in people who exhibit donor specific antibodies) • DSA levels post-transplant/imlifidase treatment • Kidney function • Mortality • Graft failure • AMR events • Incidence of viral and bacterial infections	Outcomes presented are those where clinical data are available from clinical trials of imlifidase and prioritised to clearly show the safety and efficacy of imlifidase	The ERG noted that several outcomes were not presented, including time to rejection, time to next RRT, or time to rebound concentration of DSAs post-transplant. Presentation of these outcomes would have informed a clearer link between clinical evidence and the economic model.

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• Time to next RRT; type of next RRT • Time to rebound concentration of DSAs post-transplant; proportion of patients requiring treatment of DSAs post-transplant • Incidence of viral and bacterial infections • Hospitalisation days • AEs of treatment • HRQoL			
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the			The ERG regarded that the NICE reference case was followed.

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	intervention will be taken into account.			
Subgroups	Recipients of kidneys from living donors; recipients of kidneys from deceased donors; low risk ('delisted') recipients of donor kidneys, non-delisted recipients of donor kidneys; degree of sensitisation in terms of antibody levels (e.g. positive microbead test, FC crossmatch, positive CDC crossmatch).	No specific subgroups considered in submission.	Given the indication, deceased donors are the main population of interest. The other listed subgroups fall outside the indication for imlifidase (living donor transplants, need for a positive crossmatch precludes 'delisted' recipients). The degree of sensitisation is not considered appropriate to subdivide beyond 'highly sensitised' (which form the main population for this appraisal) as the judgement of sensitisation is a complex area that requires clinical judgement around the patient-specific immunological profile. In addition, the SmPC for imlifidase cautions against use in patients with a T-cell CDC crossmatch positive. The company would not like to, with current evidence, recommend this population for imlifidase-enabled kidney transplantation. Therefore, further subgroups based on degree of sensitisation were not considered appropriate.	The ERG regarded that this was appropriate.
Special considerations including issues	The equality impact assessment scoping identified the following issues, according to the	As per NICE documents.	The evidence around equality issues and groups that may be impacted by the	The ERG noted that patients who have historically been disadvantaged in waiting

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
related to equity or equality	principles of the NICE equality scheme: • People who are highly sensitised (that is, people on the waiting list for organ transplantation carrying antibodies to HLA) may not be provided with the same access to transplantation and standard of care as non-sensitised people. Imlifidase may help to ensure that this gap can be narrowed further in the future. • Imlifidase may also offer highly sensitised patients in minority ethnic groups, who already have difficulty accessing a matched donor kidney. These people with protected characteristics could gain access to a donor kidney sooner and, thus, are likely to have better outcomes once transplanted. • Clinical experts at the scoping workshop indicated that one of the most common causes for a patient to be 'highly sensitised' is previous pregnancy.		availability of imlifidase will be presented	times for a kidney transplant may benefit from treatment with imlifidase. The extent of this effect will be better understood once the impact of changes to the KOS in 2019 are known. The ERG noted a lack of clarity in whether issues of equality will arise as a result of the introduction of imlifidase under the current KOS. Alterations to the scheme may be required to prevent preferential treatment of patients who are eligible for imlifidase.

Abbreviations: AEs, adverse events; AMR, antibody mediated rejection; CDC, complement dependent cytotoxic; DSA, donor specific antibodies; eGFR, estimated glomerular filtration rate; ERG, Evidence Review Group; FC, flow cytometry; HLA, human leucocyte antigens; HRQoL, health-related quality of life; KOS, kidney offering scheme; N/A, not applicable; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; QALY, quality adjusted life year; RRT, renal replacement therapy; SmPC, summary of product characteristics

3. CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of imlifidase for preventing kidney transplant rejection in adults with stage 5 CKD awaiting a kidney transplant from a deceased donor, who have a positive crossmatch and are highly sensitised with HLA antibodies.

The ERG has critiqued the details provided on:

- Methods implemented to identify, screen and data extract relevant evidence;
- Clinical efficacy of imlifidase;
- Safety of imlifidase.

A detailed description of an aspect of the CS is provided only when the ERG disagrees with the company's assessment or proposal, or where the ERG has identified a potential area of concern that the ERG considered necessary to highlight to the Committee.

3.1. Critique of the methods of review(s)

The company undertook a systematic review, limited to a range of specified study types, assessing the clinical effectiveness of imlifidase in people with ESKD awaiting kidney transplant compared to people on long-term dialysis. Overall, the ERG found, due to poor reporting and unnecessarily complicated search methodology by the company, that it was unable to assess if the company's systematic literature review was of reasonable quality and likely to have identified all relevant studies. A summary of the ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem is presented in Table 6.

Table 4: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D Section D.1.1	The searches for population and intervention are broadly appropriate. However, the decision to limit the search by study type is a surprising one given the paucity of evidence and the newness of this technology. Adverse events and clinical effectiveness were included in the same search strategy. Since searches were limited by study design it is possible that papers reporting adverse events may have been missed, due to exclusion of

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		additional publication types such as case reports. The decision to use restrictive study type limits reduced the number of results considerably e.g. from 3,536 to 1,288 in the original PubMed searches. Relevant papers are likely to have been missed from the systematic review. The Grey Literature searches (Table 5) cover a good range of sources, but only one clinical trials register has been searched (clinicaltrials.gov). Furthermore, this search has been 'Filtered by Completed studies' which means that any ongoing trials will not have been identified. For example, these searches do not pick up Study 14 in the search results; this study would have been picked up if searches had included ongoing studies. The decision to filter by completed studies only is hard to fathom.
Inclusion criteria	Document B, Section B.1.1, Table 1; Appendix D, Section D.1.1.2	Broadly appropriate. As can be seen from the company's specified inclusion criteria, the population was narrower than specified the NICE scope i.e. the CS only included highly sensitised patients who were awaiting kidney transplantation from a deceased donor and who were unlikely to be transplanted under the kidney offering scheme. However, dialysis (HD/PD) was the only specified comparator, in line with the company supposition that dialysis is the only alternative treatment option for patients. Data received by the ERG from NHSBT shows that a significant minority of patients do not receive dialysis[9], and this was not considered by the company's review. Five studies (reported in 11 publications) were identified by the company for inclusion: four uncontrolled, open label studies (reported in 10 publications, including two pooled analyses), and one Phase 1 FIH study. The company also provided unpublished data linked to the four uncontrolled, open label studies. In respect of adherence to the inclusion criteria, the ERG noted that the included Phase 1 study had been conducted in a population of healthy male volunteers. While the company acknowledged in the CS (Document B, Section B.2.10.7), that the population of healthy volunteers was "*less directly relevant to the population of interest*", the ERG considered that the study should have been excluded as it did not meet the population criterion specified in the inclusion criteria. One ongoing trial was also identified (Section B.2.11); however, the ERG noted that this was not identified via systematic methods as searches for ongoing trials were not conducted (restricted to completed studies). See Section 3.2 and subsections for summary of the evidence included in the CS and detailed critique.
Screening	Appendix D, Section D.1.1.1	It was unclear to the ERG if screening was performed independently by two reviewers. The company stated that

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		'all searches were performed by two independent reviewers' as opposed to screening for titles and abstracts and full text screening.
Data extraction	Appendix D, Section D.1.1.1	It was unclear to the ERG whether data extraction was performed independently by two reviewers, although the company stated that a randomly selected sample of excluded studies was verified by a third reviewer.
Tool for quality assessment of included study or studies	Document B, Section B.2.5; Table 13	The company used the ROBINS-I tool to evaluate the risk of bias in the included studies. The version used was not entirely appropriate for use in single-arm trials, however broadly captured the key risk of bias issues. There was a lack of clarity in the judgements made, which were not sufficiently resolved during clarification. Generally, the ERG considered the company to have underestimated the risk of bias of the included trials (see Section 3.2.2 for the ERG's assessment).
Evidence synthesis	Document B, Section B.2.8	The company did not undertake formal evidence synthesis, though two pooled analyses of patients from trials were presented. The statistical methods used for these analyses relied on naïve pooling, which the ERG regarded was justified by low sample sizes.

Abbreviations: CS, Company submission; ERG, Evidence Review Group; FIH, first in human; NICE, National Institute for Health and Care Excellence; ROBINS-I, Risk Of Bias In Non-randomised Studies - of Interventions

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation

The company's clinical evidence review identified 10 publications relevant to the decision problem (CS appendix D, p. 21-22); these publications reported clinical efficacy and safety evidence from four, uncontrolled, open-label studies and two pooled analyses of patients from across the studies. The company also reported data from two further unpublished pooled analyses: a pooled analysis of the patients the company considered to be most relevant to the decision problem (the ERG termed this the 'decision problem cohort') and a pooled analysis of all those patients in the included trials who received at least one dose of imlifidase (the ITT or safety set).

An overview of the included studies is provided in Section 3.2.1.1. The reported pooled analyses were as follows:

- Jordan *et al.*, (2017)[11]: analysis included data from 33 participants, of which 25 had received a transplant during Studies 02, 03, and 04

- Winstedt *et al.*, (2019)[15] (conference abstract): analysis included data from 46 participants with varying levels of anti-HLA antibodies and DSA who were transplanted following imlifidase treatment (Studies 02, 03, 04, and 06).
- Unpublished data[16]: analysis included data from 25 participants from Studies 02, 03, 04 and 06 that were considered most relevant population to UK clinical practice; i.e. a group designated 'unlikely to be transplanted' defined as a cPRA of ≥95% (MFI ≥3,000), deceased donor kidney offer and positive crossmatch test. This analysis included a subset of participants included in the analysis conducted by Winstedt et al. (2019). This is the analysis the ERG regarded as the decision problem cohort.
- Unpublished data: analysis of all participants who received at least one dose of imlifidase from across the included trials (Studies 02, 03, 04, and 06) (i.e. the ITT/safety set).

While the company considered these 10 included studies and the pooled analyses to be relevant to the decision problem for this appraisal, the ERG nevertheless considered that the study characteristics and outcome data in the CS were patchily reported across the studies and analyses.

The company also included one further study publication, which reported data from a Phase 1 (first in human) study in healthy male volunteers (11-HMedIdeS-01 [Study 11]) (Winstedt *et al.*, 2015[17]). The ERG considered that this study did not meet the inclusion criteria for the review and should have been excluded from the company's SLR (Table 4). The ERG further considered that the adverse event data from this study reported in the CS (CS, Document B, Section B.2.10.7), and in detail within a separate appendix of the CS (Appendix F), was irrelevant to the decision problem for this appraisal. The ERG therefore advises the committee to disregard these data in the CS, and provide no detailed critique of this study in its report.

In addition, the CS makes references to one additional trial that was not identified by their clinical review: an ongoing five-year, long-term, follow-up study of adults treated with imlifidase prior to kidney transplantation, which includes participants from the imlifidase kidney transplantation studies (Studies 02, 03, 04 and 06) (17-HMedIdeS-14 [Study 14] [NCT03611621]). The ERG noted that this study had not been identified in the company's review as searches they conducted within clinicaltrials.gov had been restricted to completed studies (Table 4). As the company include data from this study in the CS, and the populations

are consistent with the decision problem for this appraisal, the ERG considered that this study should have been identified and included in the company's review.

The ERG conducted its own search for ongoing trials (terms kidney AND imlifidase), and was confident that there were no other ongoing trials in the target population. The ERG noted that this study fulfils objectives as part of the risk management plan to address the limited safety data in the context of the conditional marketing authorisation (CMA) granted by the European Medicines Agency (EMA).

The ERG noted that the inclusion criteria and searches used for the company's clinical review were restricted to studies that evaluate imlifidase. While this approach was consistent with the scope for this appraisal, the ERG considered that the lack of comparative or matched studies in the included studies indicates that the inclusion of naïve comparison data would have greatly augmented the evidence base. As such, the ERG would have liked to see an expansion of the inclusion criteria to include outcome data for patients receiving the comparator treatment (i.e. dialysis; see Key Issue 3).

3.2.1. Study methodology

3.2.1.1. Study design

The study designs of the five studies that the ERG considered to address the decision problem for this appraisal (Study 02, Study 03, Study 04, Study 06 and Study 14) included in the company's systematic literature review (SLR) of clinical evidence are summarised in the CS (Document B, Table 8 and Document B, Section B.2.11) and key summary information are provided in Table 5. The ERG presented these study designs to inform understanding of the decision problem cohort.

The four original studies (Study 02, Study 03, Study 04, and Study 06) were uncontrolled, open-label, Phase 2 or Phase 1/2 studies. The company stated that a randomised controlled trial (RCT) had not been feasible in this indication due to considerations around the nature of imlifidase treatment and the associated kidney transplant; specifically, in the context of the original trial design, it would require the randomisation of patients to a desensitisation strategy that is highly unlikely to be successful within the necessary timeframe for deceased donor transplantation (CS, Document B, Section B.2.2). Additionally, the scarcity of donor organs and the differences in kidney allocation systems between countries were noted by the company as a further barrier to conducting a RCT (CS, Document A, Section A6). Given the rarity of the

condition, and the lack of appropriate comparator strategy the ERG considered the use of uncontrolled, open-label study design to be appropriate in the absence of robust alternatives. None of the studies were conducted in the UK: the studies were conducted in France (Study 06), Sweden (Studies 02, 03, and 06) and the USA (Study 04 and 06).

As the primary outcomes for the four original studies were safety and the ability to achieve a crossmatch conversion, follow-up was relatively short: final follow-up ranged between 64 days and 180 days. However, this means that long-term outcomes important to evaluating the success of transplant were not evaluated. The company stated that their ongoing trial Study 14 will identify long-term data, including quality of life data that is otherwise missing from the CS. However, to date, only a subset of the planned sample has been included, and limited interim data were reported in the CS (study expected completion December 2022, results December 2023).

All studies were conducted prior to the CMA for imlifidase was awarded, and the interventions and populations included in the studies varied somewhat from the CMA. These issues are noted in Sections 3.2.1.2 and 3.2.1.3.

Table 5: Included studies

Study identifiers (Location) [Study Status]	Intervention(s)	Phase	Participants enrolled	Study objectives	Design (Duration)	Population
13-HMedIdeS-02 (**Study 02**)[1,] NCT02224820 (Sweden[11,18-20]) [Completed]	Imlifidase 0.12 mg/kg 2 doses, 0.25 mg/kg 1 dose; 0.25 mg/kg 2 doses	2	8	Effective dose, PK, PhD, and safety	Uncontrolled, open-label, dose escalation (64 days)	Men and women (age ≥18 years) with Stage 5 CKD; Ab against ≥2 HLA antigens
13-HMedIdeS-03 (**Study 03**)[1] NCT02475551 (Sweden[11,19]) [Completed]	Imlifidase 0.25 mg/kg / 0.50 mg/kg	2	10	Effective dose, PK, PhD, and safety	Uncontrolled, open-label, dose escalation (180 days)	Men and women (age ≥18 years) with Stage 5 CKD intended for transplantation with ≥1 anti-HLA Ab ≥3,000 MFI
14-HMedIdeS-04 (**Study 04**) [1] NCT02426684 (USA[11,21-24]) [Completed]	Imlifidase 0.24 mg/kg	1/2	17	Efficacy; safety	Uncontrolled, open-label (180 days)	Sensitised (cPRA >50%) men and women (age 18-70 years) with Stage 5 CKD, awaiting kidney transplantation, prior desensitisation attempt(s), detectable DSA(s) or positive crossmatch tests
15-HMedIdeS-06 (**Study 06**) [1] NCT02790437 (Sweden[11,25], France, USA) [Completed]	Imlifidase 0.25 mg/kg (second dose if required)	2	19	Efficacy, PK, PhD, and safety	Uncontrolled, open-label (180 days)	Kidney transplant patients, in whom prior desensitisation was unsuccessful, or effective desensitisation highly unlikely. Positive crossmatch with living or deceased donor
17-HMedIdeS-14 (**Study 14**) [1] NCT03611621 [Ongoing]	Not applicable		Up to 46 planned enrolment	Efficacy, safety and HRQoL	Long-term follow-up, observational study of transplanted patients after imlifidase administration (5 years)	Patients who have undergone kidney transplantation after imlifidase administration in Studies 02, 03, 04, and 06

Abbreviations: Ab, antibody; CKD, chronic kidney disease; cPRA, calculated panel-reactive antibodies; DSA, donor specific antibodies; HLA, human leukocyte antigen; HRQoL, health-related quality of life; MFI: mean fluorescence intensity; PhD, pharmacodynamic; PK, pharmacokinetic

Notes:

[1,] Pooled analyses combining data from these studies were available: combined data from 33 participants in Studies 02, 03 and 04 [11](25 of which were transplanted) (Jordan et al., 2017); combined data from 46 transplanted participants in Studies 02, 03, 04, and 06 [15]; combined data from 25 participants defined as "highly unlikely to be transplanted" from Studies 02, 03, 04 and 06 (unpublished data) (i.e. decision problem cohort); and combined data from all participants who received at least one dose of imlifidase from across the included trials (Studies 02, 03, 04, and 06) (i.e. the ITT/safety set).

3.2.1.2. Trial populations

The decision problem cohort was a subgroup drawn from Studies 02, 03, 04 and 06, of the most relevant patients to the target population for imlifidase (very highly sensitised [cPRA of ≥95% (MFI ≥3000)], who are 'unlikely to receive a transplant'. All patients included in the cohort also had a deceased donor kidney offer and positive crossmatch test. The company noted that the criteria chosen for this analysis were not tied to existing guideline or specific clinical practice, and were selected to best meet the CMA for imlifidase and the expected European patient population. Within the 54 participants from across the trials, 25 met these criteria. Clinical advice received by the ERG noted that this population covered those most likely to benefit under the current KOS. As a marker of sensitisation, the cPRA and cRF give comparable ratings for sensitivity in the same patient; the cPRA, is also a 'virtual' test against the HLA profile of donors and commonly used outside of the UK. The ERG did not consider the use of cPRA rather than cRF in the trials to affect generalisability of the populations to the UK.

Criteria used in component studies

Eligibility criteria for each of the component studies that informed the decision problem cohort were provided in the main CS (Document B, Table 8). Inclusion criteria for all studies specified that adults (aged ≥18 years), with chronic kidney disease or ESKD; however, the eligibility criteria differed at several important points between the studies. Because the breadth and strength of sensitisation in terms of number of different anti-HLA antibodies and level of those antibodies, respectively, predict likelihood of successful desensitisation or kidney paired donation, earlier Studies (02 and 03) were less matched to the decision problem than later Studies (04 and 06).

- **Transplantation waiting list and dialysis.** Studies 02 and 03 required patients to be in dialysis. Whereas Study 03 required an available compatible donor (living or deceased) as an inclusion criterion, Studies 04 and 06 required patients to be awaiting transplantation. Study 04 further required that patients have a non-HLA identical donor with a positive crossmatch at point of transplantation, and Study 06 further required that patients have a live or deceased donor with a positive crossmatch test.
- **Sensitisation.** Studies 02 and 03 required some degree of sensitisation, described as identified anti-HLA antibodies, whereas Study 04 required cPRA ≥50% on three

consecutive samples and Study 06 required HLA antibody status with PRA ≥80% on two consecutive samples over three months.

- **Prior trials of desensitisation.** Study 06 specifically included patients who had previously undergone desensitisation unsuccessfully or in whom effective desensitisation was highly unlikely.

There were more exclusion criteria in Study 03 than in Studies 04 and 06. However, the ERG noted that most of these exclusion criteria are generally considered contraindications for renal transplantation. The ERG also noted that donor tissue/cells for the crossmatches investigated in Study 02 were derived from healthy subjects and that blood donors with HLA phenotypes against which the study patients had antibodies (donor-specific antibodies) were used for crossmatch analyses in a CDC crossmatch assay.

Generalisability of component studies

Because of the limitations in the populations of the component studies, the ERG agreed with the company that it was appropriate to conduct a separate subgroup analysis specifically for the target population considered in the submission. Moreover, clinical advice received by the ERG agreed that patients in Studies 04 and 06 were closest to the corresponding UK population of highly sensitised patients unlikely to receive any compatible kidney transplant, as compared to patients in Studies 02 and 03. The ERG considered this was broadly true, but noted that in Study 06, 3/19 subjects (16%) were reported to have cPRA <80%, i.e. not fulfilling the definition of being highly sensitised. Further, two of the participants in Study 04 had neither any DSA with MFI >2,000 nor a positive B-or-T-cell crossmatch to their respective donors, in spite of high cPRA (87.8% and 99.6% respectively) (CS, Document C, p.112).

3.2.1.3. Intervention characteristics and background care

The intervention characteristics used across the included studies are reported in Table 6. Across Studies 02, 03, 04 and 06 imlifidase was administered as an IV infusion; over at least 15 minutes. As Study 02 and Study 03 were dose-finding trials, not all participants in the CS received the licensed dose of imlifidase (0.25 mg/kg, with a second dose administered if indicated). The specific doses received by patients in the included trials are summarised in Table 6. At clarification [question A8], the company stated that all participants in the total transplant population (n=46) and in the decision problem cohort (n=25) received the licensed dose of imlifidase; or, if not, "generally" received a dose that was comparable (e.g. a dose of 0.24 mg/kg, or a dose of 0.50 mg/kg where not indicated by a crossmatch test). The ERG was unable to provide comment on whether a dose of 0.24 mg/kg is indeed equivalent in efficacy and safety to a dose of 0.25 mg/kg, as insufficient data was available. However, the ERG did not consider there to be major concerns with the variation in dose across studies or pooled analyses. The company stated that [redacted] of patients in the ITT/safety set across the included studies received a second dose of imlifidase (CS Doc B, p.13). The ERG considered whether the proportion of patients requiring a second dose would be greater in the decision problem cohort due to their higher levels of sensitisation and clinical advice to the ERG was that this remains uncertain.

Patients in Study 02 did not receive a transplant as part of the trial protocol, and therefore the single participant (1/8, 12.5%) who received a transplant during follow up did so incidentally. Across the included studies, a minority of patients who received a transplant received kidney from a living donor, which is not consistent with the CMA for imlifidase (Study 03: 2/10 [20%] patients transplanted; Study 06 5/18 [27.8%] patients transplanted). Living donor transplants may be associated with improved transplant outcomes, largely due to the benefits of being able to time kidney retrieval to maintain a low CIT. None of these patients were included in the pooled analysis of the decision problem cohort, but are included in the remaining three pooled analyses[11,15,16].

Table 6: Dose groups and participants exposed

Study	Dose groups	Administration	Participants exposed by dose group	Dose vs CMA[f]	Transplant
Study 02[a,b]	0.12 mg/kg; 0.25 mg/kg;	IV over 15 mins before transplantation	3 received 0.24 mg/kg (as 2 x 0.12	Mostly (3/8 patients received	1/8 (12.5%) (deceased donor)

Study	Dose groups	Administration	Participants exposed by dose group	Dose vs CMA[f]	Transplant
	0.50 mg/kg; 1.0 mg/kg		mg/kg); 2 received 0.25 mg/kg (as 1 x 0.25 mg/kg); 2 received 0.50 mg/kg (as 2 x 0.25 mg/kg); [redacted][c]	0.24mg/kg, 2/8 received 2 doses of 0.25mg, and [redacted])	
Study 03[a,d]	0.25 mg/kg; 0.50 mg/kg	IV over 15 mins Transplantation day (DD) or day before transplantation (LD)	5 received 0.25 mg/kg (as 1 x 25 mg/kg) / 5 received 0.50 mg/kg (as 1 x 0.50 mg/kg)	Consistent	10/10 (100% (8/10 [80%] deceased donor)
Study 04	0.24 mg/kg	IV over 15 mins 4-6 hrs before transplantation	17 received 0.24 mg/kg (as 1 x 0.24 mg/kg)	Partially (all patients received 0.24 mg/kg, which the company consider to be equivalent)	17/17 (100%) (all deceased donor)
Study 06	0.25 mg/kg[d]	IV over 15 mins	15 received 1 x 0.25 mg/kg (as 1 0.25 mg/kg); 3 received 0.50 mg/kg (as 2 x 0.25 mg/kg[e]); [redacted]	Mostly (1/19 received a partial dose)	18/19 (94.7%) (13/18 [72.2%] deceased donor)
Pooled analysis: decision problem cohort	Unclear	IV over 15 mins	NR	Stated to be consistent, though numbers not provided.	25/25 (100%) (all deceased donor)

Abbreviations: CMA, conditional marketing authorisation DD, deceased donor; IV, intravenous; LD, living donor; MA, marketing authorisation; vs, versus

Notes: **a** Dose escalation study; **b** Dose escalation in Study 02 was performed by doubling the chosen doses for each dose group with the anticipated doses 0.12 mg/kg (Group 1), 0.25 mg/kg (Group 2), 0.5 and 1.0 mg/kg given once or twice (Groups 3 and 4). Doses could be adjusted after evaluation of the previous dose group. The two highest doses were optional and not used; **c** [redacted]; **d** Patients in the first dose group received one IV dose of 0.25 mg/kg imlifidase (Day 0) and the second dose group received one dose of 0.50 mg/kg after evaluation of the safety and efficacy in the first group. Optional higher dose groups included 1.0 mg/kg; 2.0 mg/kg. Dose escalation to a higher group will be based on safety and efficacy evaluation of previous dose groups; **e** Dose 1, Day 0, Dose 2, 2 days after first dose if first dose was not effective and considered safe (after evaluation of efficacy and safety data for first 3 participants at Day 28); **f** Imlifidase should be administered at a dose of 0.25mg/kg, within 24 hours prior to transplantation. One dose is adequate for crossmatch conversion in the majority of patients but if needed a second dose can be administered within 24 hours after the first dose.

Across all studies, prior to imlifidase administration participants were pre-treated with glucocorticoids and antihistamines. In addition, treatment with IVIg (2 g/kg) and rituximab (1 g), was used for some patients, and routine post-transplantation prophylactic antibiotic use was broadly consistent across the trials; although antibiotic regimens varied between the trials. The use of induction therapies in the studies could be used at the discretion of the treating clinician where indicated. Clinical advisors to the ERG advised that the broader immunosuppressive regimens used in the included trials were generally consistent with UK practice.

3.2.1.4. Statistical methods used in included studies

Statistical methods throughout the CS were primarily descriptive, eschewing significance testing. The company describes the statistical analysis of the four component studies as being primarily descriptive, relying on summary tabulations. Similarly, analysis did not stratify by centre or country. The ERG regarded that given the uncontrolled design of these studies and the use of small numbers of patients, this was an appropriate choice. Definition of study groups, including full analysis sets and safety analysis sets, was also consistent between studies. As is expected for the analysis methods described, very little inferential testing was presented. While this was appropriate for the methods used, the lack of variance data precluded a more direct assessment of treatment benefit and its consistency.

Analysis methods for pooled samples (including the decision problem cohort) were not presented. Consideration of the manuscript corresponding to Jordan et al. (2017) suggested the analysis did not stratify by study, using a naïve pooling method. This is unlikely to be a major problem given small numbers and similar protocols between studies. Statistical methods for analysis of the decision problem cohort were not explicitly presented in the CS, but appeared to follow a similar pattern to Jordan et al. (2017)[11]. Survival curves drawing on data from the decision problem cohort were generated using a standard Kaplan-Meier estimator, though presentation of summary statistics from these curves was scant.

3.2.2. Quality appraisal of included studies

Using the ROBINS-I, the company reported an overall moderate risk of bias rating for all the included studies. During clarification (clarification question A3), the company clarified that this rating was applicable to all outcomes. The company rating was driven by a moderate risk of bias rating for the confounding domain, reflecting that outcome data may be affected by confounding that could not be fully accounted for in the analysis. During clarification (clarification question A4), the ERG requested that the company provide the confounders that were considered in this

rating, to which the company advised that the rating was given under the assumption that there may be unknown confounders, but they did not consider any confounders to impact on the: "*primary study outcomes and the main outcomes related to the ability for transplant to be conducted (elimination of donor specific antibodies (DSAs) and crossmatch conversion)*" (clarification response A4, p.4). The ERG was also unaware of potential confounders towards the likelihood of crossmatch conversion and the rebound of HLA antibodies, and agree with the company's conservative approach. However, the ERG considered the risk of confounding to post-transplant outcomes to be high, as many factors are known to influence transplant outcome (e.g. time on dialysis, CIT, patient age and health state, donor demographics, previous transplant rate etc).

The company rated all other domains as being at a low risk of bias (i.e. the selection of participants, delivery of interventions, attrition rate, outcome measurement, and outcome reporting bias). In general, the ERG agreed with the company ratings, although were concerned about varying levels of MFI used across the studies to indicate that a clinically meaningful reduction in anti-HLA antibodies has occurred. The ERG was aware that there is no standardised threshold for the interpretation of MFI levels, though clinical advice to the ERG was that levels of MFI below <4,000 indicate an acceptable threshold for transplant (also supported by Keith & Vranic 2016[26]). The company variously use thresholds between 1,100 and 3,000 across studies to report their results, without citation or explanation of change, though the ERG suspect that lower values of MFI may have been selected as MFI levels at baseline in the included patients were also generally low (cut-off MFI >2000). The ERG was therefore concerned for the presence of reporting bias in this outcome. In addition, the ERG considered the reporting of clinical efficacy data in the CS to be inconsistent across the included trials and pooled analyses, and therefore cannot exclude the possibility that clinical data in the CS has been 'cherry-picked' to present an advantageous view.

On the basis of the ROBINS-I tool, the company conclude that the evidence base for all outcomes is at a moderate risk of bias, which is considered to reflect that "the study provides sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial". The ERG disagreed with the company rating, and consider that the risk of bias for the included studies varied across outcomes due to the reasons outlined above. In summary, the ERG considered that the trial primary outcome of crossmatch conversion as tested using FACS or CDC may be considered at moderate risk of bias, within the context of these outcomes nevertheless being reported in uncontrolled trials (the limitations of which are

discussed further below, and in Key Issue 4. Crossmatch conversion according to MFI levels and all outcomes following transplant were considered to be at a high risk of bias. In the CS, the company did not comment on the potential quality issues associated with their pooled analyses (the analysis of the decision problem cohort [n=25]; the Jordan et al. [2017][11] analysis; all transplanted patients [n=46], and the ITT/safety set [n=54][17]). At clarification the company were asked to comment on this [clarification question A6], and they stated that they considered the overall risk of bias of the combined analyses to be equivalent to the individual trials (i.e. moderate), though they considered the larger sample sizes to be a strength. The ERG considered that more detailed consideration of the appropriateness of pooling the trials, bearing in mind the variation in study designs and populations in the included studies, would have been informative for the ERG. Pooled data drawing on sources with varying methods adds to the risk of confounding in the data, and the ERG considered that the interpretation of the data was complicated by the need to bear in mind the mix of study samples, settings, and intervention characteristics involved.

The company acknowledged that data from single-arm trials, no matter how well conducted, are associated with significant limitations. In the context of this appraisal, and in addition to the issues raised in quality assessment, the principal limitation of using data from single arm trials in technology appraisal is that an external dataset is necessary for comparison of treatment effects, such that conclusions can be drawn about a) if an effect is associated with the intervention and b) the magnitude of that effect (Hatswell et al. 2016[27]). In the CS, the company provided none of the typical methods for providing an external dataset (e.g. historical control; matched analysis); rather, the company provided background literature and clinical expert opinion to present the case that without a transplant (and treatment with imlifidase), the target population would have poorer outcomes. While the ERG agreed that outcomes for patients are likely to be worse if they remain on dialysis compared to if they receive a transplant, the ERG contest that understanding the magnitude of this difference is nevertheless informative. These data would not only inform the validity of the company's economic evaluation, but would also be informative for decisions surrounding the management of the KOS, and for clinical decision-making, where the balance of risks and benefits of transplant are integral to patient choice. The evidence selected by the company for this purpose did not appear to have been identified systematically by the company, such as through a systematic literature review. Further, the company did not state the way in which clinical advisors to the company provided their input; for example, whether a standard elicitation process (such as the SHeffield ELicitation Framework

[SHELF]) was used. As a consequence, the ERG cannot exclude the possibility of 'cherry-picking' in the selection of evidence for comparison by the company. In the ERG's consideration of the clinical outcome data in Section 3.2.4, the ERG hand searched for evidence that may be used for comparison and interpretation of the data. However, this approach is also limited, as it was not possible for the ERG to conduct a systematic search for literature, and it's likely that the evidence identified is not comprehensive, and may not be representative. In conclusion, the lack of any matching dataset, and the lack of rigour in the identification of naïve comparison data, meant that the ERG cannot draw firm conclusions about the magnitude of the clinical effects reported.

3.2.3. Baseline characteristics

This section reviews the baseline characteristics of the decision problem cohort (see Table 7Appendix A). Pooled baseline trial characteristics from transplant patients[17] (n=46) were provided by the company, and are summarised and critiqued in Appendix A of this report.

The 25 patients in decision problem cohort were drawn from Study 03 (n=2), Study 04 (n=12), and Study 06 (n=11). Patients were aged between [redacted] years of age, all diagnosed with Stage 5 ESKD and on dialysis, and received a deceased donor transplant during the trial. Of these patients, [redacted] were women, [redacted] were men and [redacted]. The ERG noted that the [redacted] of patients in the decision problem cohort included some younger patients who are frequently seen in UK clinical practice (for example, patients with more aggressive primary renal disease occurring at a younger age (who may have earlier need for re-transplant due to recurrence of medication non-adherence), and women who have had children.

Most patients ([redacted]) had undergone at least one previous kidney transplant, with [redacted] ([redacted]) patients having received multiple transplants (mean number of previous transplants was [redacted].The ERG considered this was similar to patients from the trials in other subgroups (see Appendix A), and clinical advisors considered that the number of previous transplants was broadly in line with what would be expected in clinical practice. The ERG noted that mean time on dialysis ([redacted]) seemed long compared to recently published data on waiting times in clinical practice (median waiting time approx. 36 months)6. Clinical advisors to the ERG stated that waiting times are typically longer for highly sensitised patients (and can be up to 10 years), which would be in alignment with what would be expected in UK clinical practice. However, the ERG was aware that data on waiting times for the decision

problem cohort following changes to the KOS are not yet known. Furthermore, clinical advice to the ERG highlighted the rate ([redacted]) of cardiovascular disease in the included population, which was considered to be higher than would be expected for this population, though this may be explained by the inclusion of hypertensive patients in this category.

Table 7. Demographics of the decision problem cohort

		Total (n=25)
Age (years)	Mean (SD)	[redacted]
	Range	[redacted]
Sex, n (%)	Female	[redacted]
	Male	[redacted]
Race, n (%)	White	[redacted]
	Black	[redacted]
	Other	[redacted]
Weight (kg)	Mean (SD)	[redacted]
	Range	[redacted]
Body mass index	Mean (SD)	[redacted]
	Range	[redacted]
Mean time on dialysis before transplant (years)	Mean (SD)	[redacted]
Hepatic impairment at inclusion	N (%)	[redacted]
Cardiovascular disease at inclusion	N (%)	[redacted]
Diabetes at inclusion	N (%)	[redacted]
Autoimmune disorder at inclusion	N (%)	[redacted]
Number of previous renal transplants	0, n (%)	[redacted]
	1, n (%)	[redacted]
	2, n (%)	[redacted]
	3, n (%)	[redacted]
Deceased donor status	N (%)	[redacted]
Organ storage	Simple cold storage, n (%)	[redacted]
	Hypothermic machine perfusion, n (%)	[redacted]
Cold ischaemic time, hours	Mean (SD)	[redacted]
	Range	[redacted]
Time on dialysis;	Mean (SD)	[redacted]
No. of previous transplants	Mean (SD)	[redacted]
Number of DSA at baseline	Mean (SD)	[redacted]

		Total (n=25)
Pre-treatment MFI of immunodominant antigen	Mean (SD)	[redacted]
	Median	[redacted]
cPRA	Mean (SD)	[redacted]
	Median	99.9
	Range	[redacted]
Pre-treatment FACS crossmatch, N(%)	B-cell positive/T-cell negative	[redacted]
	B-cell negative/T-cell positive	[redacted]
	B-cell positive/T-cell positive	[redacted]

Abbreviations: cPRA: calculated panel reactive antibodies; DSA: donor specific antibodies; FACS: fluorescence-activated cell sorting; MFI: mean fluorescence intensity; NR, not reported; SD: standard deviation

Notes:

* [redacted]

Source: CS, Document B, Section B.2.8.2.1, Table 17 and Table 18

All patients were very highly sensitised with a median cPRA of 99.9%; the ERG noted that the range of cPRA starts at [redacted] (Table 7). Patients in the decision problem cohort had a mean of [redacted] DSAs, and a mean MFI of [redacted]. Based on the information provided, the ERG agreed with the company's assertion that these characteristics were consistent with a population where it would be difficult to find a suitable transplant in current UK practice. All patients had a positive FACS crossmatch to a deceased donor before imlifidase treatment (CS, Document B, Section B.2.8.2.2, Table 19). The ERG noted that [redacted] patients included from Study 06 had a confirmed B-cell negative, T-cell positive crossmatch test at baseline. In the CS, the company propose caution in using imlifidase to reverse a T-cell positive crossmatch prior to kidney transplant in this group; the ERG was therefore unclear whether the evidence from the CS is therefore generalisable to patients with a T-cell crossmatch only.

The decision problem cohort for this appraisal is a new target indication, and therefore the ERG was unable to identify any independently published demographic data on the typical UK characteristics of this group for comparison with the trial populations (CS, Document B, Section B.2.8.2.1, Table 17). However overall, clinical advisors to the ERG confirmed that the baseline demographics of the decision problem cohort were broadly similar to those patients who would be expected to receive imlifidase in UK clinical practice.

3.2.4. Clinical effectiveness results

The ERG considered that the clinical effectiveness results presented in the CS were muddled and difficult to identify and interpret, particularly regarding the reporting of data from the pooled analyses, which were not consistently presented for each outcome. For clarity and to aid the committee, the ERG has summarised the clinical data for the decision problem cohort in an appendix to this report (Appendix B).

As noted in Section 2.4, evidence was not presented for multiple scoped outcomes (time to graft failure; time to rejection; time to next renal replacement therapy; time to rebound concentration of antibodies; hospitalisation days; and health-related quality of life (HRQoL). During clarification (response to clarification question B11), the company presented simplified Kaplan-Meier plots for graft survival, on the basis of data from Study 14. While ongoing, this trial has data on graft survival up to three years post-transplant, which the ERG considered would have greatly augmented the company's clinical evidence if presented in full. On the basis of the included studies, the company only presented discrete event data for graft failure and rejection, which is less informative than time-to-event data.

The ERG was also concerned that discrete event data following transplant were generally presented in samples only including patients who exhibited a crossmatch conversion and transplant following treatment with imlifidase, rather than the ITT population. As this approach limits efficacy data to those who respond to imlifidase treatment, this may give a biased view of the benefits of imlifidase.

In the following sections (Section 3.2.4.1 to Section 3.2.4.6), note that the study population informing reported outcomes is the decision problem cohort (n=25), unless otherwise stated

3.2.4.1. Efficacy on crossmatch conversion (ability to create a negative crossmatch test in people who exhibit donor specific antibodies)

The rate of crossmatch conversion is the company's primary outcome in the CS, and is the only outcome uniquely associated with the efficacy of imlifidase (as opposed to outcomes that capture the subsequent benefit of transplant). Despite this, the evidence for the rate of crossmatch conversion following treatment with imlifidase is significantly limited. Methods for evaluating a crossmatch conversion varied across trials, and the ERG was aware that different methods for assessing crossmatch vary in their accuracy and interpretation. The ERG was

therefore concerned with pooled estimates of the rate of crossmatch conversion provided by the company that included multiple different measures, including in the pooled analysis of the decision problem cohort. The ERG was also surprised in the limited rate of crossmatch testing conducted over the included studies: the ERG was aware that the FACS and CDC crossmatch tests are most commonly used in the UK, but only 2/46 (4.3%) of transplanted patients were evaluated using CDC, and only 31/46 (67.4%) of transplanted patients in the included trials were evaluated for a crossmatch conversion using the FACS (please note that the latter of these figures was provided by the company following submission of this report, but could not be validated by the ERG).. MFI levels evaluated using SAB assay were more commonly presented by the company, although this data was difficult to interpret, as the company used different thresholds to demonstrate efficacy across the trials (as noted in Section 3.2.2). Furthermore, the mean change in MFI level data were not reported for all analyses, and where reported were not accompanied with variance data. Finally, not all MFI levels were reported for patients with a donor and in reference to a DSA, and therefore the importance of these data is unclear.

Based on the limited data provided, the ERG considered there to be evidence that treatment with imlifidase leads to a reduction in MFI levels in patients who are highly sensitised. In the pooled analysis of the decision problem cohort, mean MFI levels dropped from [redacted] (median [redacted]) at baseline to [redacted] (median [redacted]) post-treatment (CS, Document B, p. 83). Without variance data it's not possible to be certain of the significance of this change, however the ERG note that mean MFI levels dropped below the threshold at which MFI levels are considered to be of concern for transplant (3,000; as suggested by clinical advisors to the ERG).The company also reported the findings of an analysis restricted to DSAs with an MFI value >3,000 at baseline, which found that [redacted] and [redacted] of patients showed no DSA with an MFI >3000 at two- and 24-hours following treatment with imlifidase, respectively.

In the pooled analysis of the decision problem cohort, using all timepoints and measures of crossmatch conversion used by the company, 24/25 (96%) of patients exhibited a crossmatch conversion following treatment with imlifidase. In addition, the vast majority of patients across the included studies who received imlifidase and were evaluated using the FACS (at any time point; n=23) demonstrated a crossmatch conversion and were able to receive a transplant (21/23, 91.3% [data calculated by the ERG]). One of the patients, included in both pooled analyses, did not experience a crossmatch conversion according to FACS, but this was considered not to be clinically significant, and the transplant nevertheless proceeded. As these data are in patients who would be unlikely to receive a transplant otherwise, the ERG found this

data to be convincing of the efficacy of imlifidase, despite the limitations and the small sample size. The ERG further considered that uncertainty due to the limitations in the pooled analysis of the decision problem cohort were somewhat reduced by data from the other pooled analyses. However, the ERG nevertheless considered that a reliable estimate of the true rate of crossmatch conversion following treatment with imlifidase has not yet been demonstrated. This has implications for the company's economic model, which includes assumptions about the rate of transplant in patients who receive imlifidase (see Sections 4.2.3, 4.2.4, and 6.3.1).

Finally, the ERG noted some uncertainty about the timing of when crossmatch conversion occurred: in the included trials, the outcome was defined as a crossmatch conversion within 24 hours, with patients tested at different timepoints within that timeframe. This, contributes to the ERG's concerns about the placement of imlifidase in the treatment pathway (see Key Issue 2).

3.2.4.2. Kidney function (eGFR)

Evidence for kidney function following transplant was reported using eGFR in the decision problem cohort, though data was not available for 20% of participants (i.e. 5/25). On the basis of the data reported, the ERG considered that kidney function was comparable with average kidney function reported for a universal kidney transplant population (UKRR, 22nd report[28]). The company stated that kidney function was good or satisfactory in "all patients with a functioning kidney and available data" (CS Dcoument B., p.83), though the criteria for this statement were not stated. Kidney function data were not reported in full for the Jordan et al. 2017[11] analysis, though the company cited [29-31]several naïve comparisons and stated that patients had kidney function "in line with expectations for highly sensitised, post-transplant patients" (CS Doc B, p.80).

The company further reported rates of delayed graft function (DGF), though not in the pooled analysis of the decision problem cohort. In the pooled analysis of all transplant patients,[15] [redacted] of patients ([redacted]) exhibited DGF (CS Doc B, p. 93). Of these, kidney function was established within one week for [redacted] and within one month for a further [redacted] (the discrepancy in numbers [i.e. [redacted] patients with DGF vs. [redacted] patients whose kidney function was restored] was not explained. The company claimed that the rate of DGF in this analysis is consistent with comparable populations, though no citations were provided (CS, Document B, p.93;). A similar rate of DGF was also reported in the Jordan et al. (2017) analysis[11] (10/24 [42%]). In these patients, the company stated that all patients required dialysis until it resolved (median six days, range not provided; CS Document B p.80).

3.2.4.3. Time to graft failure

Time to graft failure was not reported in the CS for the decision problem cohort to a degree that would permit extraction and analysis. The ERG requested this during clarification (clarification question B11), but the company only provided this for Study 14. Data were presented in a Kaplan-Meier plot, with insufficient detail to calculate time to graft failure. However, the CS reports that data from Study 14, including patients from across the included clinical trials, shows a death-censored graft survival of [redacted] at two years.

In the CS, the company reported that 96.0 % (24/25; CS, Document B p.84) of patients in the decision problem cohort had a functioning graft at six months. The ERG considered these rates to be comparable to a non-sensitised population of patients[6] and improved compared to other highly sensitised populations[32-34]. It was not clear from the CS whether the one patient who did not have a functioning graft at 6 months was the patient in whom crossmatch conversion was not demonstrated (but transplant went ahead; Section 3.2.4.1).

3.2.4.4. Time to rejection; type of rejection; number of rejection episodes

The company stated that they considered overall rates of rejection to be a safety consideration and not a measure of efficacy, on the basis that they do not consider imlifidase to impact on all rejection events. The company therefore only report transplant rejection rates for the pooled analyses of all transplant patients[15] (n=46) and the ITT/safety set (n=54), and not for the decision problem cohort. Across the 46 transplant recipients in the trials, the CS reports that [redacted] patients exhibited transplant rejection as a serious adverse event (SAE; CS Document B, p.90). In the ITT/safety set, the CS reports that 1/54 (1.9%) patients exhibited a rejection that was treatment-related, though they do not elaborate on this event.

With regard to rates of AMR, the company did not clearly differentiate between the proportion of patients who exhibited chronic vs. acute AMR, and therefore the following rates are considered inclusive of both. In the pooled analysis of the decision problem cohort, 10/25 (40%) patients exhibited AMR, as confirmed by biopsy. [redacted] of these patients exhibited no clinical signs and were categorised as subclinical AMR. The company further stated that all patients were succesfully treated with standard immunosupression (CS Doc B p.85). The rate of AMR in the decision problem cohort was higher than the rate of AMR experienced in the total transplanted population and the Jordan et al. pooled[11] analysis, where the rates were 32.6% (15/46) and 20% (5/25), respectively. In the total transplanted population (n=46), the CS states that the "majority" of AMRs were resolved by six months, however the number and variation in this rate

was not reported (CS Document B, p.93). The CS notes that one patient exhibited an AMR that resulted in an immediate graft loss (CS Doc B, p.93), though the ERG was unclear if this was the only patient in the included studies to exhibit this, and in which pooled analyses this patient may have been included in. The ERG found that rates of AMR appeared to be comparable with other desensitisation regimes, where rates of AMR can range between 25% - 50%[26,35,36]. At clarification [A15], the company provided further rates of AMR in desensitised patients, which were also consistent. However, the rate of AMR in all populations is significantly higher than the rate of AMR seen across all kidney transplants, where the rate varies between 5-7%[37]. Clinical advice to the ERG highlighted concerns about the rate of AMR exhibited in the decision problem cohort, as acute AMR can be difficult to treat, and is associated with an increased risk in chronic rejection and premature graft loss.

3.2.4.5. Time to next renal replacement therapy; type of next renal replacement therapy

Time to next renal replacement therapy was not reported in the CS. During clarification (clarification question A6) the ERG requested this data, and during the clarification call (8 Oct 2020), the company offered to provide this evidence. However, in its clarification response, the company stated that these data were not evaluated in any of their trials.

3.2.4.6. Time to rebound concentration of donor specific antibodies post-transplant; proportion of patients who require treatment of rebound antibodies post-transplant

Time to event data for a rebound in donor specific antibodies after transplant, and the proportion of patients requiring treatment for the rebound in antibodies, were not reported in the CS. Given the mechanism of imlifidase and the highly sensitised nature of the target population, the absence of this outcome data is a significant limitation of the evidence base. Understanding of the timing and implications of rebound in anti-HLA antibodies is not only informative for understanding transplant outcomes in patients treated with imlifidase, but is also informative for the way in which patients with imlifidase will need to be monitored following transplant (such as the timing of DSA testing).

The company did report some scattered data on the rebound of MFI levels post-transplant; however as with the assessment of MFI levels prior to transplant (Section 3.2.4.1), the company used varying thresholds for reporting the rebound of MFI levels across the included trials. Mean and median change in MFI at various timepoints were reported for the pooled analysis of the

decision problem cohort, though without variance data, which significantly restricts their interpretability. In this group, mean MFI levels were reported to rise to [redacted] (median [redacted]) at Day 7, [redacted] (median [redacted]) at Day 14, and [redacted] (median [redacted]) at Day 30 (mean MFI levels pre-treatment were [redacted]; median [redacted]). This means that mean MFI levels were below baseline after 1 month, but above the threshold considered to be a concern for transplant after 2 weeks. The lack of variance data is particularly concerning when the company reported variation in the timing of rebound of MFI levels across patients (e.g. in the Jordan analysis[11]; CS Doc B p.78-79). The ERG considered the data to demonstrate that anti-HLA antibodies stay sufficiently low after treatment with imlifidase to facilitate transplant, but considered the data to be uninformative for understanding rebound of anti-HLA antibodies following transplant. Furthermore, clinical advisors considered the rebound in MFI levels to be a concern given the rates of rejection reported, as further information would provide guidance on the appropriate monitoring of patients following transplant.

In the following sections (Section 3.2.4.7 to Section 3.2.4.9), note that the study population informing reported outcomes is the population who received at least one dose of imlifidase (the ITT or safety set), unless otherwise stated.

3.2.4.7. Incidence of viral and bacterial infections

Clinical advisors to the ERG confirmed that infection risk is particularly important with a drug such as imlifidase because of the complete depletion of immunoglobulin. Hence, infections, particularly respiratory tract infections, are of potential concern with imlifidase treatment as these are the most common infections in patients with hypogammaglobulinemia. Clinical advisors to the ERG confirmed that pneumonia and chest sepsis are relatively common in transplant patients and would be expected to be seen in the first month following transplantation in UK clinical practice.

The company did not report the rate of infection in patients in the decision problem cohort only; and limited data was reported for the ITT/safety set (n=54) only. At clarification [A13], the ERG requested the company provide adverse event data for patients in the decision problem cohort; however, the data provided by the company did not include figures specific to the infection rate. The ERG was uncertain whether the rate of infection would be higher in more highly sensitised patients, but noted that this may be possible, and this may particularly be the case if shown that

more highly sensitised patients are more likely to require a second dose of imlifidase (Section 3.2.1.3).

In the ITT/safety set, 9/54 patients (16.7%) experienced a severe or serious infection that was assessed as being related to imlifidase; although the criteria for this decision was not reported in the CS. The total number of infections (including non-serious/severe, and those not determined to be treatment-related) was not reported. The most common treatment-related adverse events that were also infections were pneumonia (n= 3/54 (5.6%)) and sepsis (n=2/54 (3.7%)). Five AEs were reported in three patients aged ≥65 years, including one of the two incidences of sepsis, and four non-serious AEs[12]. Three (5.6%) patients developed urinary tract infection, but these were not judged as treatment-related. Based on clinical advice, the ERG agreed that while the rate of infection is relatively high, the incidence and pattern of serious or severe infections were not different from those observed in kidney transplanted patients in general, particularly early on following transplantation Clinical advisors to the ERG stated that they would expect the incidence of infections in people receiving imlifidase to be comparable with other high risk transplant patients undergoing de-sensitisation, but higher as compared to the broader transplant population. However, the single-arm nature of the included evidence, and the lack of any matched comparison data, means that it is not possible for the ERG to conclude whether the infection rate is higher with imlifidase treatment. In the interim, clinical advisors to the ERG did not consider there to be concerns about treating older patients, at higher risk of infection with imlifidase; beyond the usual considerations when assessing a patient for transplant surgery.

3.2.4.8. Mortality

No deaths were reported during the main trial period of Studies 02, 03, 04, and 06. The company stated in the CS that during longer-term follow-up, three deaths were reported (CS, Section B2.10.7, p.92); however, the number of participants and time of follow-up of this data were not reported in the CS.

The European public assessment report (EPAR[12]) indicated that follow-up data were available for 35 of 46 transplanted participants (29 of whom have been enrolled in the long-term follow-up study). Of the 35, three deaths (8.6%), occurred in imlifidase-treated participants after study completion (six months to one-year post-imlifidase treatment). In each case the cause of death was considered unrelated to imlifidase or kidney malfunction (noted as circulatory arrest, unknown cause and *Pseudomonas bacteraemia*) (CS, Section B2.10.7, p.92 and CS, Document

C [EPAR]). Of note, from the EPAR, is that the three deaths occurred in the decision problem cohort. Clinical advisors suggested that the deaths observed in the highly sensitised group may be attributable to a higher cumulative burden of immunosuppression associated with these patients receiving more treatment in the past; but acknowledged that the very small number of participants involved prevents any firm conclusion. The lack of a matched comparison also prevents drawing conclusions about whether the mortality rate is comparable to typical kidney transplant patients.

3.2.4.9. Adverse effects

In the CS, rates of adverse events (AEs) were generally only provided for the safety/ITT analysis set (n=54). At clarification (clarification response A12), the ERG requested AEs data for the decision problem cohort, but the data provided were limited (see Table 8).

[redacted] in both the decision problem cohort and the ITT/safety set experienced at least one AE following treatment. A significant minority of these were considered by the company to be related to treatment with imlifidase ([redacted] in the decision problem cohort and 20/54 [37%] of patients in the ITT/safety set) but the company criteria for this distinction were unclear: the company stated that if causality information was missing, the event was assumed to be related to imlifidase (CS Doc B, p. 87-88), however the ERG still considered this to be unclear. The vast majority of treatment-related AEs were stated to have occurred in the first 30 days following treatment (19/54, 35.2%; CS Doc B, p. 89).

[redacted] in the decision problem cohort exhibited a severe adverse event, labelled as 'non-SAE', but the nature of the event was not reported. Moreover, the rates of SAE in this group were not reported, and the ERG was therefore unclear how the distinction between severe and serious was made, and how many serious AEs occurred in the decision problem cohort. The ERG considered this to be a notable omission. In the ITT/safety set, the company reported the majority of patients who received imlifidase experienced at least one SAE (38/54, 70.4%), with a total of 112 SAEs reported (CS Doc B, p. 90). The most common SAEs were transplant rejection ([redacted]); Section 3.2.4.4) infections (Section 3.2.4.7) and increased blood creatinine ([redacted]). The company determined that SAEs in 11/54 (20.4%) patients were related to treatment with imlifidase; however, again the criteria for this decision was not reported. In the 11 patients, 12 SAEs were reported, of which 3/12 (25%) were not classed as infections (transplant rejection, myalgia, and infusion-reaction).

The ERG did not consider the rate of discontinuation due to AEs reported by the company to be informative for the decision problem cohort, since all patients were included in this analysis after successful treatment and transplant. However, in the ITT/safety set, the ERG noted that [redacted] required a drug withdrawal or dose interruption (CS Doc B, p. 87), and [redacted] of patients experienced an infusion reaction to imlifidase that prevented receiving the full therapeutic dose and were unable to receive a transplant.

Table 8: Summary of adverse events

Patients experiencing the following	Decision problem cohort (n = 25)	Total safety set (n = 54)
≥1 AE	[redacted]	54 (100.0%)
≥1 TEAE	[redacted]	54 (100.0%)
≥1 treatment-related AE	[redacted]	20 (37.0%)
Any mild AE	NR	6 (11.1%)
Any moderate AE	NR	4 (7.4%)
Any severe AE	NR	8 (14.8%)
Any life-threatening AE	NR	2 (3.7%)
≥1 treatment-related TEAE	[redacted]	19 (35.1%)
Severe treatment-related TEAE (non-SAE)	[redacted]	3 (5.6%)
≥1 TEAE leading to study discontinuation	0	NR
≥1 TEAE leading to treatment discontinuation	0	2
Fatal AE	[redacted]	0

Abbreviations: AE, adverse event; NR, not reported; SAE, serious adverse event; TEAE, treatment emergent adverse event

Source: CS, Document B, Section B.2.10.1, Table 24; and clarification response A12 Table A12.1 and Table A12.2 and A13

Clinical advisors to the ERG advised that in addition to infections, this patient population may be susceptible to malignancies, particularly skin and those that are virally-associated, such as lymphoma and cervical. While the ERG considered that malignancies are unlikely to be directly associated with imlifidase as it is a short acting drug, the literature suggests that malignancy is more likely in this population due to the frequent maintenance of higher-levels of immunosuppression, which is required to reduce the risk of allosensitisation and which contributes to the risk of solid organ tumours in the longer term. Within the short timeframe of the included studies, it is not possible to determine whether treatment with imlifidase may lead to an increased risk of malignancy, and this remains an outstanding area of uncertainty.

On the basis of the safety data reported, the ERG did not consider it possible to conduct a comprehensive appraisal of the safety of imlifidase in the decision problem cohort. In the ITT/safety set, the ERG noted that the vast majority of SAEs were transplant rejections and infections; these issues are discussed more broadly in Sections 3.2.4.4 and 3.2.4.7, however to reiterate, it is unclear from the evidence available whether the rates of infection and rejection reported are comparable with other populations. It appears that the rate of SAEs other than infections and rejection is low. There is evidence that a small minority of patients may experience infusion reactions that will delay or prevent receiving a therapeutic dose of imlifidase, which may prevent transplant. Finally, the ERG noted that one of the reasons underlying the conditional nature of the EMA licence for imlifidase is the need for further data on adverse events following treatment with imlifidase and subsequent kidney transplant. The CMA mandates that the company collect this data, which will be partially informed by the ongoing Study 14 trial, in addition to other ongoing and planned studies.

3.2.4.10. Subgroup analyses

No further subgroup analyses were conducted by the company, due to concerns about the sample size available. The ERG agreed that the sample size in the included trials would be insufficient to compare effects between subgroups of interest.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No additional trials were included to inform an indirect comparison.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparisons were undertaken.

3.5. Additional work on clinical effectiveness undertaken by the ERG

The ERG performed hand searches to identify external data points corresponding to outcomes reported in the CS; where identified, these are cited in the clinical effectiveness section. No further work was undertaken by the ERG.

3.6. Conclusions of the clinical effectiveness section

The evidence base for the clinical effectiveness of imlifidase in the target population is highly limited, as it is consisted of single-arm trials with small sample sizes, and there is considerable

inconsistency in the trial populations, interventions, and outcomes reported. The evidence is at a moderate or high risk of bias, with an unknown risk of confounding to the outcome data. The lack of a matched comparison dataset, or rigorously identified external data to facilitate naïve comparisons, undermines the interpretation of transplant outcomes in patients receiving imlifidase. Furthermore, outcome data in the CS is poorly reported; unclear, selective, and inconsistent across trials and analyses.

Despite the above significant and broad limitations in the clinical evidence base, evidence for crossmatch conversion was convincing: patients across the included studies tested for conversion using FACS (n=25) demonstrated an almost total conversion rate, with all patients who received the licensed dose of imlifidase subsequently receiving a transplant. In the pooled analysis of the decision problem cohort, a 96% rate of crossmatch conversion (across measures) with subsequent transplant is a clinically meaningful result, and suggests that treatment with imlifidase could be transformative for the care of these patients.

A major caveat to the above is the lack of medium to long-term data on transplant outcomes following treatment with imlifidase. Generally speaking, there was no conclusive evidence that transplant outcomes were worse than would be seen in other de-sensitised patients, and in some cases were comparable with the general kidney transplant population.

However, clinical advice to the ERG was that the rate of AMR reported in the decision problem cohort (40%) was a concern, as acute AMR is a known predictor of poorer transplant outcomes, including graft failure and chronic rejection. These outcomes may not have been picked up in the short-term follow-up of the included studies, and therefore the lack of long-term data in this population is a significant limitation in understanding the potential risks of transplants that have been facilitated by imlifidase in the target population.

There was no evidence that treatment with imlifidase results in unacceptable adverse events, though the ERG noted that there remains uncertainty about whether the rates of AEs would be comparable in the target population, and whether the rates of rejection and infection are comparable with other transplant recipients. In the absence of further evidence, clinical advisors to the ERG advice that all patients within the licensed indication who are considered sufficiently robust to undergo a kidney transplant may be eligible for imlifidase; however, that procedures for monitoring patients for AEs after transplant is as yet unclear.

4. COST-EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

The company carried out a SLR, using a single search strategy with a range of search filters, to identify existing cost-effectiveness evidence, HRQoL evidence, and cost and resource use evidence in adults with CKD awaiting a kidney transplant from a deceased donor, who have a positive cross match and are highly sensitised with HLA antibodies. A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 9.

Table 9: Summary of ERG's critique of the methods implemented by the company to identify health economic evidence: Cost-effectiveness studies

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix G, Section G.1.1	These searches use a cost-effectiveness filter, but it does not appear to be a tested one such as those by CADTH[38] or SIGN[39]. Therefore, some results may have been missed.
Inclusion criteria	Appendix G, Section G.1.3	Broadly appropriate. The company considered imlifidase and long-term dialysis (HD or PD, haemodiafiltration) for the treatment of CKD awaiting a kidney transplant from a deceased donor, who have a positive crossmatch and are highly sensitised with HLA antibodies. Dialysis (HD/PD) was the only specified comparator, in line with the company supposition that dialysis is the only alternative treatment option for patients. The ERG noted the population in the CS was narrower than specified the NICE scope i.e. the CS only included highly sensitised patients who were awaiting kidney transplantation from a deceased donor and who were unlikely to be transplanted under the KOS. No prior cost-effectiveness models were identified.
Screening	Appendix G (cross reference to Appendix D, Section D.1.1.1)	No detail provided in Appendix G. A cross reference to the methods reported in Appendix D was given. It was unclear to the ERG if screening was performed independently by two reviewers (refer to critique in Table 4).

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data extraction	NA	No methods were specified in Appendix G. However, no cost-effectiveness studies were identified in the searches. This was not unexpected given the specialist nature of the technology, as expected, no existing models were found.
QA of included studies	NA	

Abbreviations: CADTH, Canadian Drug and Technologies in Health; CKD, chronic kidney disease; CS, Company Submission; ERG, Evidence Review Group; HD, haemodialysis; HRQoL, health-related quality of life; KOS, kidney offering scheme; NA, not applicable; NICE, National Institute for Health and Care Excellence; PD, peritoneal dialysis; QA, quality assessment; SIGN, Scottish Intercollegiate Guidelines Network

Table 10: Summary of ERG's critique of the methods implemented by the company to identify health economic evidence: Health-related quality of life

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods / ERG comment
Searches	Appendix H, Section H.1.1	These searches use a cost-effectiveness filter, but it does not appear to be a tested one such as those by CADTH[38]. Therefore, some results may have been missed.
Inclusion criteria	Appendix H, Section H.1.3	Broadly appropriate. The company included studies evaluating imlifidase and any relevant comparator reporting a HRQoL outcome in adults with CKD awaiting a kidney transplant from a deceased donor, who have a positive crossmatch and are highly sensitised with HLA antibodies. The ERG noted, however, the population in the CS was narrower than specified the NICE scope i.e. the CS only included highly sensitised patients who were awaiting kidney transplantation from a deceased donor and who were unlikely to be transplanted under the KOS. Although the broader focus in this context was considered appropriate given the paucity of evidence in the narrower population. The company identified two studies that contained health-related quality of life data in people with CKD, and provided a tabulated summary (Appendix H, Section H.1.4, Table 6). Refer to Section 4.2.7 for the ERG's assessment of identified evidence.
Screening	Appendix H (cross reference to Appendix D, Section D.1.1.1)	No detail provided in the CS (Appendix H). A cross reference to the methods reported in Appendix D was given. It was unclear to the ERG if screening was

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods / ERG comment
		performed independently by two reviewers (refer to critique in Table 4). Study selection was documented in a PRISMA flow diagram (Appendix H, Section G.1.3, Figure 1).
Data extraction	Appendix H, Section H.1.4	No detail provided. The company summarised details for the identified studies (CS, Appendix H, Table 6).
QA of included studies	Not reported	No detail provided in Appendix H. No formal critical appraisal of the studies was conducted; however, the company did, provide an assessment of the consistency of each study with the reference case (CS, Appendix H, Table 6).

Abbreviations: CADTH, Canadian Drug and Technologies in Health; CKD, chronic kidney disease; CS, Company NICE, National Institute for Health and Care Excellence; Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; KOS, kidney offering scheme; NA, not applicable; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QA, quality assessment

Table 11: Summary of ERG's critique of the methods implemented by the company to identify health economic evidence: Cost and healthcare resource identification, measurement and valuation

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods / ERG comment
Searches	Appendix I, Section I.1.1	These searches use a cost-effectiveness filter, but it does not appear to be a tested one such as those by CADTH[38]. Therefore, some results may have been missed.
Inclusion criteria	Appendix I, Section I.1.3	Broadly appropriate. The company included studies evaluating imlifidase and any relevant comparator reporting resource utilization, treatment costs, productivity, utility and caregiver disutilities in adults with CKD awaiting a kidney transplant from a deceased donor, who have a positive crossmatch and are highly sensitised with HLA antibodies. The ERG noted, however, the population in the CS was narrower than specified the NICE scope i.e. the CS only included highly sensitised patients who were awaiting kidney transplantation from a deceased donor and who were unlikely to be transplanted under the KOS. Although the broader focus in this context was

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods / ERG comment
		considered appropriate given the paucity of evidence in the narrower population. The company provided a tabulated summary of six studies identified in the searches.
Screening	Appendix I (cross reference to Appendix D, Section D.1.1.1)	No detail provided in the CS (Appendix I). A cross reference to the methods reported in Appendix D was given. It was unclear to the ERG if screening was performed independently by two reviewers (refer to critique in Table 4). Study selection was documented in a PRISMA flow diagram (Appendix I, Section I.1.3, Figure 1).
Data extraction	Appendix I, Section I.1.4	No detail provided. The company summarised details for the identified studies (CS, Appendix I, Table 6).
QA of included studies	Not reported	No detail provided in Appendix I. No formal critical appraisal of the studies was conducted.

Abbreviations: CADTH, Canadian Drug and Technologies in Health; CS, Company Submission; ERG, Evidence Review Group; HLA, human leukocyte antigen; KOS, kidney offering scheme; NA, not applicable; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the ERG

4.2.1. NICE reference case checklist

Table 12: NICE reference case checklist

Systematic review step	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The model does include a disutility for carers, which the ERG was in full agreement with. Relevant impacts on the wider transplant network are not included, and are highlighted as a key issue and in a sensitivity analysis by the ERG
Perspective on costs	NHS and PSS	-
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	-
Time horizon	Long enough to reflect all important differences in costs or	A lifetime horizon (57 years) is used, which is appropriate given

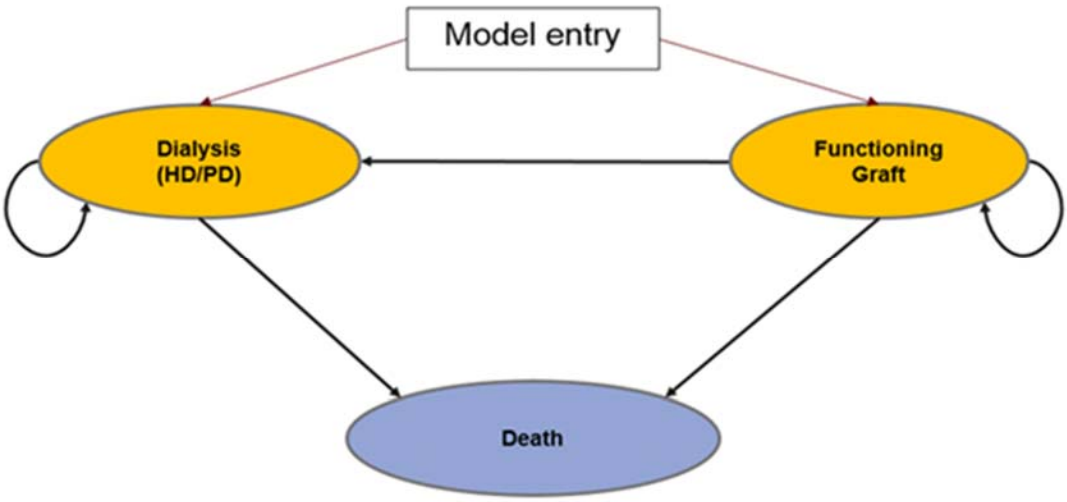
Systematic review step	Reference case	ERG comment on company's submission
	outcomes between the technologies being compared	the up front costs and downstream benefits of the technology
Synthesis of evidence on health effects	Based on systematic review	Although not based on systematic review, the evidence for imlifidase includes all relevant data, and appear reasonable
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	-
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	-
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The company identified literature of reasonable quality but with some methodological issues. Since the company submission however, a systematic review has been published which the ERG have identified and incorporated into the model The source of data for carers was also of questionable relevance, and has been updated by the ERG
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	-
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	-
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	-

Abbreviations: EQ-5D, EuroQol 5-dimension; ERG, Evidence Review Group; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

A three state *de novo* partitioned survival economic model was submitted by the company (this was incorrectly labelled as a markov model by the company). The model diagram is presented in Figure 2

Figure 2: Company's model diagram



Abbreviations: HD/PD, haemodialysis/peritoneal dialysis
Source: CS, Document B, Section B.3.2.2, Figure 8

In the company model, patients entered the model in either the functioning graft health state (imlifidase) or dialysis state (comparator).

- When in the functioning graft health state, patients could exit to dialysis (driven by parametric curves derived from the published 'iBox' predictive model on graft survival) or death (with rates driven by parametric curve fits to the imlifidase clinical trial data).
- From dialysis, patients die at rates determined by their age, derived from UK Renal Registry (UKRR) data.

Within each health state, patients accrue relevant costs and benefits, with utilities attached to each health state (including a disutility for caregivers in the dialysis health state).

The model structure was subject to several limitations due to its simplicity. Firstly, the model does not include the potential for subsequent transplant from either functioning graft or dialysis

health states. Secondly, the patients are unable to transition from dialysis to transplant or from no-treatment to receive either dialysis or transplant. However, given the lack of available data to inform transitions, the ERG considered the model structure appropriate for the decision problem.

4.2.3. Population

The model considered people with ESKD who are 'highly sensitised', which the company defined in the corresponding clinical evidence as ≥95% cRF rather than the typical definition of ≥85% cRF (Section 2.1). For the intervention arm, patients must also have received a transplant with imlifidase treatment.

The ERG considered this population different to the scope of the appraisal as it is based on patients in the intervention arm having *received a transplant* rather than all those who *received imlifidase*; i.e. it does not consider an intention to treat (ITT) perspective in including patients who were treated, but did not receive the desired outcome. There are likely to be some patients ([redacted]out of [redacted] in the clinical trial program, based on the company's clarification response A13) who receive imlifidase but, due to infusion related reactions or failure to achieve a negative crossmatch, are not able to go on to transplant. This assumption limits the conclusions that can be made in the model which assumes that 100% of the patients who are administered imlifidase demonstrate a negative crossmatch and receive a subsequent transplant, which the ERG does not think accurately represents the population eligible to receive the treatment.

4.2.4. Interventions and comparators

4.2.4.1. Imlifidase and transplant

The intervention in the model was imlifidase received at the licensed dose. Imlifidase is dosed according to weight with those weight ≤44 kg receiving one vial, those between 44 kg and 88 kg receiving two vials and those weighing ≥88 kg receiving three vials. The model accounted for different weights of patients (and thus required different numbers of vials), by calculating the number of vials required to treat the trial population. Although this was not necessarily the same weight distribution as seen in the general population, the ERG considered it to be a good proxy of the patient population.

Some patients may require a second dose to achieve a negative crossmatch, which has been included by the company in the economic model. The CS reports [redacted] of patients required a second dose in the clinical studies, although the ERG was unclear as to whether this

percentage corresponds to the ITT population (all who received imlifidase), the population who received imlifidase and went on to receive a transplant or the decision problem cohort ('unlikely to be transplanted' patient group). It is possible that the more highly sensitised patients may be more likely to require a second dose and as a result, the company's estimated proportion of [redacted] is potentially too low.

However, as mentioned in Section 4.2.3, the population modelled considers all those who received imlifidase and a transplant, as opposed to those who received imlifidase only (in line with the NICE scope). To capture these issues, the ERG has assigned a proportion of patients in the intervention arm to receive imlifidase but no subsequent transplant, and thus receive dialysis instead (modality distribution aligned with the comparator arm). The proportion of patients to undergo transplant following imlifidase is calculated by dividing the number of patients who discontinued imlifidase (and therefore did not receive the full dose) by the total number of patients (52 out of 54).

One patient did not achieve a negative cross match with a FACS test but went on to receive a transplant regardless (based on a negative result from a virtual crossmatch test and clinical opinion) however, the company's modelling approach does not have the functionality to capture this patient as a failed crossmatch conversion. Despite the lack of a negative FACS crossmatch test, as the patient received a negative virtual crossmatch and received a subsequent transplant, the ERG has opted to include the patients as a 'success' within their preferred base case analysis. However, the ERG notes that this patient could also have been considered a 'failure' to convert and therefore, varies this in a scenario analysis by multiplying the proportion of patients to receive the full dose (52/54) by the proportion to achieve a negative FACS crossmatch (51/52).

This resulted in an estimated 96.3% (52/54) in the ERG base case, and 94.4% (52/54 * 51/52) in a scenario analysis, of patients to be transplanted following imlifidase infusion which was incorporated into the ERG base case with alternative proportions assessed in the sensitivity analysis to explore the impact of this assumption.

4.2.4.2. Dialysis

The comparator in the model is dialysis with no opportunity to receive a transplant. In the submission, finding a donor for these patients is described as 'extremely difficult' (CS, Document A, Section A.1.2, Paragraph 2); however, is not said to be impossible. The source cited in the company submission (Jordan *et al*. 2015[40]) states

"Currently, only 6.5% of patients with a panel reactive HLA antibody (PRA) levels above 80% [i.e. highly sensitized (HS)] receive a transplant each year"

This was further supported by expert clinical input to the ERG which indicated that while patients would have difficulty in finding a match, they would not necessarily always fail to find one, with an example provided by a clinical expert of a patient who recently received a transplant despite having a 100% crossmatch. Sensitivity should therefore be seen as (greatly) reducing the likelihood of an acceptable match with any individual kidney; however, in the context of approximately 2,350 kidneys available from deceased donors nationally each year [6], the ERG notes that the chance of a highly-sensitised patient receiving a transplant should not be zero. This forms a part of the ERG additional analyses detailed in Section 6.3.3 based on data provided by NHSBT.

Furthermore, the chosen comparator in the company's analysis is dialysis, as opposed to "established clinical management" which was specified in the NICE scope. The ERG requested and received data from NHSBT[9] on the treatments received by highly sensitised patients on the transplant waiting list. The data from NHSBT provided to the ERG is presented in Table 13 along with the patient distribution used by the company in the model, discussed in Section 6.2.

Table 13: Company and NHSBT dialysis status for cRF ≥99% transplant waiting list patients[9]

Dialysis status	Company distribution (UKRR 21st Annual Report)	NHSBT distribution (cRF ≥99%)
Haemodialysis	78.2%	73.9%
Peritoneal dialysis	21.8%	9.7%
Not on dialysis	-	15.6%
Not reported	-	0.8%

Key: cRF, calculated reaction frequency; NHSBT, National Health Service Blood and Transplant; UKRR, United Kingdom Renal Registry.

The ERG notes that the comparator in the model should allow a proportion of patients to receive no dialysis to align with current practice (as seen in Table 13). In order to capture this in the analysis, the ERG has assigned the proportion of patients seen in the NHSBT data to the modalities in the model, including allowing a proportion to receive no treatment. However, the ERG also considers that as patients' age and duration of disease increases, it is likely that they will require treatment. Therefore, after 3 years (6 model cycles) all patients alive in the

comparator arm are assigned dialysis treatment with the proportions redistributed to reflect those seen in the NHSBT data. At this point, 88.4% of patients are assigned to haemodialysis with the remainder (11.6%) assigned to peritoneal dialysis.

A further consideration relates to the decision problem faced and the potential trade-offs elsewhere in the transplant systems. Demand for donor kidneys outstrips supply, despite initiatives to increase the number of kidneys available. This scarcity is referenced by the company multiple times in the CS (e.g. CS, Document A, Section A.6, CS, Document B, Section B.2.5, and Section B.3.11), as justification for why a randomised design was not used. The implication of this, however, is that should the decision be made to give a patient imlifidase (and a transplant), that kidney would otherwise be given to a patient elsewhere in the healthcare system who did not have a positive crossmatch and thus did not require the use of imlifidase to achieve transplantation. Furthermore, in having spent less time on dialysis, and not having antigens, it is possible (and potentially likely at the aggregate level) that the alternative recipient may achieve a better outcome from transplantation than the imlifidase patient. This consideration is discussed within Key Issue 1.

The ERG takes no position in whether recognising this opportunity cost, should be the base case, and therefore simply presents the results of an analysis exploring the net losses to the health system through the use of imlifidase in Section 6.3.11.

4.2.5. Perspective, time horizon and discounting

The model considers an NHS perspective for a lifetime time horizon. Although the model extends to 57 years (114 cycles) from the time of transplant where patients would be aged 102 years, in the company base case 95% of patients have died in the imlifidase arm by 40 years and 99% by 49 years. Over this time period both costs and benefits (QALYs and LYs) are discounted at 3.5% per year in line with the NICE methods guide. The ERG considered both the time horizon and approach to discounting to be appropriate.

In terms of the perspective, there are two categories that are not typically seen in technology appraisals:

- The inclusion of costs relating to patient transport (Section 6.3.6).
- The inclusion of carer quality of life (Section 6.3.5).

The ERG agreed that conceptually these areas are appropriate for consideration and in line with the NICE methods guide, though disagreed with the implementation undertaken by the company for both items, which forms a part of the further work performed in Section 6.2.

4.2.6. Treatment effectiveness and extrapolation

The treatment effectiveness and extrapolation relate to two separate areas in the company economic model.

The treatment effectiveness relates to the ability of imlifidase to allow patients to undergo treatment. The evidence for this is taken from pooled data in the clinical program (Section 3.2.4). This data was then naively pooled to inform the probabilities of achieving transplant – although not formally meta-analysed, the ERG accept this approach as the differences between the protocols are not expected to be highly-influential. The issues raised around patients treated but not receiving transplant in Section 4.2.3 applies here, and is discussed further in Section 6.3.1.

4.2.6.1. Graft survival

To extrapolate the effects of imlifidase once transplant has been achieved, outcomes are taken from the decision problem cohort up to six months, and then estimated using the 'iBox' predictive model[41] for the following 10 years. The ERG considered the iBox to be a high-quality predictive model which was developed using a dataset of approximately 3,500 French transplant patients from four centres. Various patient characteristics are used from this dataset of mixed patients to predict graft survival for 10 years from six-months post-transplant. To this, the company has then fitted a variety of parametric curves (approximately, but not exactly) following NICE DSU TSD14. The company chose a Weibull model to extrapolate graft survival with the iBox predictions. Based on the visual fit to the data and justification provided by the company, the ERG believes the Weibull provides a reasonable fit to the iBox data. Although all curves fit the predicted data, uncertainty exists in how well these perform beyond the predicted outcomes, with additional structural uncertainty in how well the iBox predicts in this highly sensitised patient group – this latter point is explored by the ERG in Section 6.3.9.

In particular the ERG was concerned with the difference in the proportion of patients with a prior transplant between the population in this appraisal and the iBox population to whom data was fitted (60% and 15%, respectively). Clinical advice to the ERG noted a prior transplant as a negative prognostic factor; however, this does not appear to be included in the published iBox

predictive model (which likely had low discriminative ability for a coefficient linked to prior transplant, given the low numbers and high variability). A second concern relates to the proprietary model which is used to generate predicted survival – as stated by the company in response to clarification question B5:

> *"The iBox analysis was conducted by the Paris Transplant Group (who developed and own the iBox technique/data) for Hansa. iBox relies on proprietary data that Hansa does not have access to, and so the response that Hansa is able to provide in this regard is, unfortunately, limited."*

Overall therefore, the ERG found the company's preferred approach to predicting graft survival to be reasonable, noting the limitations around the use of the iBox model, and without any mechanism to investigate the predictive model or understand how it was generated.

4.2.6.2. Overall survival with a functioning graft

Overall survival in patients with a functioning transplant (graft) was extrapolated from all patients who received imlifidase and a transplant in the included trials (n = 46) using a variety of parametric curves with the exponential model selected for the base case. Based on the visual fit, AIC and BIC, the ERG find the company's choice of extrapolation model to be reasonable.

The company also included the option to model from the decision problem cohort population however, did not include this as their base case due to low patient numbers. Three patients died following transplant, all of whom were in the decision problem cohort. As patient numbers in this group are limited (n = 25), these deaths are highly influential on the results. An exponetial model was selected by the company to extrapolate the overall survival of the target population which the ERG believe is a reasonable selection based on visual fit and AIC/BIC. The ERG considered the use of the 'all imlifidase' group to inform overall survival for those with a functioning graft to be reasonable due to limited sample size however, explore the impact on the ICER in a scenario analysis (Section 6.4.1.1).

4.2.6.3. Dialysis overall survival

To extrapolate the survival of dialysis patients which is followed by all comparator patients and imlifidase patients upon graft failure, the company has performed a series of calculations using data obtained from the UKRR. Although this increases risk as patients age (rather than being linked to time on dialysis), this increased risk is factored in via a standardised mortality ratio and

appears to produce plausible estimates. The ERG has concerns with the implementation of the risk ratio (Section 6.3.9) as the risk can fall at five-year time points due to the use of five-year age bands; however, the ERG considered this a minor issue for the modelling.

The company also provided a secondary source of dialysis survival from the European Renal Association (ERA) which is presented as a scenario analysis (Section 6.4.1.1).

4.2.7. Health-related quality of life

No relevant health-related quality of life instrument was included in the clinical studies, therefore the utilities used to populate the cost-effectiveness model were taken from the literature.

Two studies were identified in the company's systematic review of h[42]ealth-related quality of life evidence (Section 4.1). For the dialysis and transplant states, values were taken from Liem *et al*. (2008)[42], a systematic review (and meta-analysis) of EQ-5D utility values in the literature which included (for the health states relevant to this appraisal); transplant (seven studies), haemodialysis (seven studies) and peritoneal dialysis (six studies). The company also included a secondary set of utilities from Li *et al.* (2017)[43], which used data from all 72 UK transplant centres collected as a part of a clinical study. The company's justification for using Liem *et al.* over Li *et al*., is that the study by Li *et al.* included patients on the waiting list for transplant rather than exclusively on dialysis.

The ERG disagreed with the company on the most appropriate data source for utility values due to the following reasons:

- Although the ERG considered the Liem *et al.*[42] study to be of good quality, the searches were conducted in September 2006, which necessarily excluded patient data published in the last 14 years. Not only does this exclude large volumes of data, it is also the most relevant data due to care evolving over time (both for transplant, and dialysis).
- The study by Liem *et al.*[42] has methodological issues when used in cost-effectiveness modelling. By synthesising values from different sources (only two studies contribute values to each of the three health states), there is a high risk of confounding by indication; i.e. different patients being included in each of the health states, and the different methodologies and treatment settings influencing the results. This can be seen with the transplant health state utilities, where patients are on average approximately 10 years

younger than the patients in dialysis health states (which the company then attempt to account for).

- On careful reading of the Li *et al.*[43] study, of the 1,070 patients classified as on the waiting list for transplant, only 98 were pre-dialysis (the main, but not only, reason given by the company for not using the data was that it includes non-dialysis patients). Furthermore, an analysis is provided (Table 5 of Li *et al.*) where a utility regression is given including (negative) coefficients for how long a patient has been on dialysis. This would appear to overcome the objection of the company to the data from Li *et al.* which otherwise would appear more suitable for use in the UK as it was performed using data from all UK transplant centres.
- Furthermore, data provided to the ERG by NHSBT[9] demonstrated that not all highly sensitised patients (>99%) are on dialysis treatment; of the 491/495 patients whose dialysis status is known, 77 (15.7%) were not on dialysis.

The ERG was conscious that the issue of confounding by indication is likely to be present in both data sources, and that by definition in not having received a transplant the dialysis patients are likely to be a more severe group. This would mean that patient utility would likely not reach the same levels as those in the (cross-sectional) literature if they did receive a transplant. To this end the ERG performed additional targeted literature searches, identifying a systematic literature review by Cooper *et al.*, published in September 2020[44] (after the company had made its submission). This included longitudinal estimates of the impact of transplant; i.e., how much difference a transplant made to the same individual, rather than comparing across groups. This systematic review supersedes that identified by the company, and in the view of the ERG, provides more plausible estimates avoiding the aforementioned methodological issues.

Section 6.3.4 details the additional work performed by the ERG in implementing the utilities from the systematic review by Cooper *et al.* (which the ERG has selected for its base case).

The CS included a carer disutility which was derived by taking a Japanese study of carers, and looking at the difference from the index value for an age and sex matched (Japanese) population, then multiplying these by the ratio of Japanese: UK utility norms. Although the ERG agreed with the concept of a carer disutility, the way in which the company calculated it appears questionable due to the number of different sources and assumptions used. Instead, the ERG identified a study of informal carers quality of life based on 195,000 responses to the English

GP Patient Survey, which provides a disutility of 0.03 based on the difference between carers and non-carers[45]. Although not a driver of the model, the ERG believed this value to be more appropriate

In the CS utilities are set to reduce with age, which the ERG believed to be the correct approach. However, the ERG preferred to adjust the model population for age and sex using decrements from Table A of Kind *et al*[46]. This is as the source used by the company relied upon an age squared term, which without taking in to account the distribution of ages, would be an approximation rather than a precise value; should the calculation be performed correctly however, the ERG would be perfectly happy with the original source (Ara & Brazier 2010[47]).

4.2.8. Resources and costs

The majority of costs in the model were taken from NHS reference costs, 2017–2018. While the ERG noted that a more recent NHS reference cost source is available (2018–2019), the company have inflated all costs to 2019 using the PSSRU inflation index[48]. The key costs of note in the model are: imlifidase, transplant proceedure, transplant maintenance and dialysis. Adverse events from both imlifidase and transplant were included, though of minor importance.

The ERG discussed the costs applied in the model in the following sections; however, considered the costs used by the company to be broadly appropriate, with the exceptions of:

- Following imlifidase infusion, crossmatch test costs are not accounted for
- The costs associated with transplant-related maintenance for the first six months are not appropriately applied
- The high cost of hospital-paid transport for haemodialysis patients
- No DdsaSA test costs are explicitly applied throughout transplant maintenance or graft loss

These areas are discussed in the further work performed by the ERG (Section 6.2).

4.2.8.1. Imlifidase

The list price of imlifidase is £135,000 per vial, with a simple patient access scheme (PAS) of [redacted] applied within the base case analyses in the model. Imlifidase is dosed based on weight, with one vial required for patients weighing ≤44 kg, two for those weighing between 44–88 kg and three for those weighing ≥88 kg. The proportions assigned to each number of vials in the

model was calculated from the baseline weights of the patients from the key imlifidase trials with the majority [redacted] receiving two vials. Following the initial dose, a second dose may be required if a negative crossmatch has not been achieved. The model assumes [redacted] of patients will require a second dose, based on the proportion requiring a second dose within the clinical trials.

No administration costs are applied in the model as the CS states: "T*he 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.*" (CS, Document B, Section B.3.5.1.1, p129).

The ERG considered this a reasonable assumption and notes that the inclusion of 30 minutes of nurse time to administer imlifidase is unlikely to have a great impact on the results.

The ERG understood that following an imlifidase infusion a crossmatch test would be administered to evaluate whether the patient has achieved a negative crossmatch. However, costs associated with testing for a negative crossmatch were not applied within the economic model. The ERG understood there are three commonly used approaches to determine whether HLA antibodies have been significantly reduced; the CDC crossmatch, FACS crossmatch, and SAB assay tests (discussed in further detail in Section 2.1). The ERG considered the exclusion of costs associated with determining whether a negative crossmatch has been achieved to be inappropriate and so, have included the cost of one FACS crossmatch test (£300 per administration of imlifidase received) in the ERG's preferred assumptions (Section 6.3.7).

The cost of imlifidase-specific comedication (prophylactic antibiotics) were included in the model as phenoxymethylpenicillin, 1 g once daily for 14 days. Unit costs were taken from eMIT 2018. Though the ERG note that updated costs were available (2019), the impact on the results is likely negligible.

4.2.8.2. Transplant

The CS used an appropriate costing for the transplantation procedure (£14,636) and subsequent care, though does not include a cost for organ retrieval or the overheads of the NHS transplant service. To explore the impact of including these costs, a crude ERG scenario was presented; however, it is not clear how these costs should be applied from the perspective of the NICE methods guide given the limited available information.

Given the number of organs transplanted, and cost of NHSBT, it would appear a mean cost of around £21,000 per organ is achieved which is discussed further and the impact on the ICER explored through sensitivity analysis in Section 6.3.10. Clinical opinion to the ERG noted that the appropriate tariff for transplantation is highly debated, this crude cost however is achieved by dividing the total yearly spend of NHSBT by the number of organs transplanted, and thus reflects an average cost which does not account for any differences in cost by organ.

4.2.8.3. Dialysis

The company's model used the percentage of patients on each type of dialysis (78.2% of patients receiving haemodialysis, with all remaining patients on peritoneal dialysis) from the UKRR 2017-18. The ERG was unable to find the proportions reported by the company within the UKRR 21st Annual Report[49]; however, did find similar values in Table 2.6 of the UKRR report. As the ERG was unsure where the values have been taken to inform the company's base case, the ERG have incorporated the values from Table 2.6 of the UKRR report for their analysis. This, however, is data for all dialysis patients, and not specifically the highly sensitised group (CS, Document B, Section B.3.5.2.2). Costs are based on NHS reference costs and appear appropriate.

In order to understand whether the proportion of patients on haemodialysis versus peritoneal dialysis was correct for the target population, the ERG liaised with NHSBT who provided the dialysis status for 491/495 of the highly sensitised patients on the waiting list. Of these patients,[9] 366 (74.5%) were undergoing haemodialysis, 48 (9.8%) peritoneal dialysis and 77 (15.7%) were not presently on any dialysis. This presented a difference from the CS, but is taken from the latest data on the highly sensitised (≥99%) group – not the wider population, and therefore, forms the basis for the ERG base case discussed in Section 6.3.3.

4.2.8.4. Medical Resource Use

Crossmatch test costs

The ERG expressed concerns regarding the exclusion of crossmatch test costs within the model in Section 4.2.8.1. To address these concerns, the ERG has applied the cost of one crossmatch test following each full dose of imlifidase. The impact of the inclusion of crossmatch test costs are discussed in Section 6.3.7.

Transplant maintenance costs

Table 45 of the CS (Document B, p. 132-134) detailed the maintenance costs associated with patients on transplant. Costs were applied each cycle and comprised of follow up appointments, blood tests and immunosuppressive therapy (tacrolimus, corticosteroid and mycohenolate mofetil). For Cycle 1 (0-6 months following transplant) and Cycle 2 (7-12 months), it was assumed that more follow up visits and blood tests would be required than in the subsequent cycles. Clinical advice provided to the ERG indicated that this would be reflective of current practice with closer follow up observed in the time soon after transplant. Table 14 presents the frequency of follow up visits and blood tests applied at each time point in the model.

Table 14: Frequency of transplant maintenance resource use

Transplant maintenance period	Frequency of follow up visits and blood tests
0 – 6 months	29
7 – 12 months	5
1 year+ (annually)	3

Following the implementation of the half-cycle correct (HCC), it appeared that the transplant maintenance costs associated with the first six months following transplant were excluded from the model. Costs associated with the 0-60 month time period were £6,882. Therefore, to correct this error, the ERG applied the costs associated with 0-6 months in Cycle 1, 7-12 months in Cycle 2 and one year+ costs from Cycle 3 onwards. This correction, along with the impact on the company's base case ICER, is further discussed in Section 5.2.

DSA testing is often used to monitor the rebound of DSAs post-transplant, and may be done at routine intervals as well as if patients show signs of organ rejection. Clinical opinion to the ERG differed on how frequently DSA monitoring would occur for patients receiving imlifidase due to the transplant being considered HLA-compatible with imlifidase use (discussed in further detail in Section 4.2.8.5). Therefore, the ERG applied the cost of one DSA test annually for patients in the 'functioning graft' health state. Furthermore, for patients not administered imlifidase who receive a transplant (as in the ERG base case), patients are assigned additional tests as the transplant is more likely to be high-risk.

Dialysis

Maintenance costs associated with dialysis include hospital-paid transportation, utilisation of conventional erythropoiesis-stimulating agents (ESAs) and nephrologist appointments. Table 46 of the CS (Document B, p. 136) provided a breakdown of costs associated with dialysis (including cost of treatment itself) applied within the model. The ERG found the costs and frequencies of resource use reported by the company to be reasonable for all but hospital-paid transport which is discussed in Section 6.2.

The cost of hospital transport for haemodialysis patients was considered by the ERG to be unreaslistically high. The data source used by the company is a survey from 2010 by the UKRR[50] which provided the type of transport used, with costs then taken from different sources (detailed in Table 46 of the CS). This led to an average weighted cost of £50 per visit, driven mainly by the 18% of patients taken by 'ambulance' for dialysis which incurrs a cost of £219 per unit. The ERG believed this to be an overestimate of NHS funded travel costs (and specifically NHS transport ambulance costs) and preferred to redistribute the 18% assigned to 'ambulance' to the other cost-incurring transport options (hospital-provided car, hospital-provided taxi, hospital-provided transport vehicle). This issue is further discussed in Section 6.3.6, along with the impact on the model results.

4.2.8.5. Adverse Events

Imlifidase

Adverse events (AEs) associated with imlifidase were applied in the first cycle of the model to reflect the one-time use of imlifidase treatment. The ERG found the company's approach to applying AE costs related to imlifidase reasonable, however, due to the application of the HCC, some patients who were administered imlifidase did not have the asociated AE costs applied. The ERG have provided a correction for this, further discussed in Section 5.2.

Transplant

AEs associated with transplant in the model include; antibody mediated rejection (AMR), delayed graft function and graft loss. Costs related to AMR and delayed graft function are applied in Cycle 1, with graft loss costs varying by the proportion of patients expected to experience a loss at Cycles 1,2,3,4 and 5+. As with imlifidase, due to the application of the HCC some patients who received a transplant did not have the asociated AE costs applied.

Additionally, the ERG note that the cost associated with graft loss Cycle 5+ has not been applied within the model, with costs associated with graft loss Cycle 4 (higher cost) applied to all cycles from Cycle 4 onwards. The ERG has provided corrections for these, further discussed in Section 5.2.

The only cost related to transplant that was identified by the ERG to be missing from the model was the DSA testing, at a cost of £55 per antigen[51]. Clinical advice to the ERG differed on the frequency of DSA testing. Two clinicians were of the view that DSA testing would occur more frequently for patients undergoing high immunological risk transplants as a form of maintenance, while the third was of the opinion that if the highly sensitised patient could receive a compatible transplant (i.e. no HLA antibodies), then the post-transplant monitoring would be the same as that of a non-sensitised patient. All clinicians were in agreement that if a decrease in graft function was suspected, DSA tests would be administered.

No DSA costs were explicitly included in the company's model, however graft loss is costed for and arguably may include the cost of DSA tests within this figure. Consequently, the ERG chose to explore the impact of DSA testing by applying the cost associated with testing for three antigens at the time of graft failure in addition to the annual test discussed in Section 4.2.8.4, as it is unknown whether costs associated with graft loss include the cost of DSA testing. The impact on the ICER when DSA costs are included is discussed in Section 6.3.12.

Dialysis

AEs related to haemodialysis and peritoneal dialysis were applied per cycle in the model. The ERG found the company's approach to applying AE costs related to dialysis reasonable however, implement an alternative distribution of patients receiving haemodialyis, peritoneal dialysis and no dialysis for analysis, which effects the costs accrued through dialysis-related AEs. Further details of the alternative dialysis distribution and subsequent effect on the ICER are discussed in Section 6.3.3.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Company's base case results

Results of the company's base case analysis are presented as an ICER for imlifidase with transplant compared to dialysis. Total and incremental costs, QALYs and life years (LYs) are presented in CS Table 54 (Document B, p. 155), replicated in Table 15 below. A [redacted] patient access scheme (PAS) of [redacted] is applied to the acquisition cost of imlifidase.

Table 15: Company base case deterministic results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*30,641*

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

The company reported a base case ICER of £30,641 for imlifidase versus dialysis, based on incremental costs of [redacted] and a QALY gain of [redacted]. The base case analysis projects [redacted] discounted Lys for patients treated with imlifidase who go on to receive a transplant, of which [redacted] were gained in the 'functioning graft' health state.

5.1.2. Company's sensitivity analysis

The CS reported a number of sensitivity analyses to explore the impact of alternative settings and assumptions, in addition to the role of parameter uncertainty within the model results. These are discussed in turn below.

The ERG noted a few discrepancies in the sensitivity analysis. The proportion of haemodialysis patients were varied using a normal distribution, rather than the stated beta distribution. Furthermore, the ERG note that the normal distribution was also used to vary the cost of kidney transplant procedure and maintenance, rather than the stated 'gamma' distribution. Finally, the ERG believed the standard errors (SEs) of the imlifidase AEs produced by the company could have been accurately predicted using the beta distribution rather than using the assumed value.

5.1.2.1. Company's one-way sensitivity analysis

The company conducted a deterministic one-way sensitivity analysis (OWSA) with the included parameters presented in CS (Document B, Table 52). The CS stated that where data were available, parameters were varied using 95% confidence intervals, otherwise upper and lower bounds were varied by a standard error of 10% of the mean (base case) value.

A tornado plot was used to present the OWSA results in the CS (Document B, Figure 20), with the ICER as the outcome of interest. The plot showed the results were most sensitive to the annual discount rates applied to outcomes and costs, utilities, initial age and the proportion of patients requiring a dose of two vials of imlifidase.

The ERG noted the inclusion of the annual discount rates for costs and outcomes in the OWSA as inappropriate due to there being no uncertainty in these parameters. Furthermore, discount rates for costs and outcomes and the proportion of vials split are not considered to be independent and therefore should not be varied independently to each other. Based on review of the submission the ERG considered the utilities and initial age to be the key drivers of the ICER in the submitted model.

5.1.2.2. Company's probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) to explore the impact of parameter uncertainty, based on each model parameters' respective distribution (CS, Document B, Table 52). 10,000 iterations were used within the PSA. The ERG found that graft survival was not included in the PSA however, which therefore underestimates the uncertainty in the decision problem.

The PSA results are summarised in the CS (Document B, Table 55 and Figure 18 (cost-effectiveness plane) and Figure 19 (cost-effectiveness aceptability curve [CEAC]). While the median and 95% confidence intervals were provided, the ERG considered only the mean PSA results to be of interest due to a need to assess the overall level of parameter uncertainty, not the 50% percentile (half-way point). Thus, the ERG will only consider the mean PSA results henceforth.

The ERG identified some errors in the probabilistic results due to the incremental costs and QALYs and the ICERs being calculated from the results of the iterations rather than from the costs and QALYs accrued for each treatment (an example for which can be seen in the CS (Document B, Table 55), 95% CI lower incremental QALYs). The ERG has corrected these

calculation errors in Table 16 below, where the probabilistic base case ICER is now seen to be similar to the deterministic result with the ERG's corrections leading to an approximate £5,000 decrease in the probabilistic ICER.

Table 16: Company mean PSA results including ERG corrections to calculations

Arm	Totals		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Company presented probabilistic base case					
Imlifidase	[redacted]	[redacted]			
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	*37,231*
ERG corrected company probabilistic base case*					
Imlifidase	[redacted]	[redacted]			
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	*31,948*

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.

Notes:

* ERG corrections to company's PSA calculation of the ICER

The company stated that at a willingness-to-pay threshold of £30,000 per QALY gained the probability of imlifidase being cost-effective versus dialysis was 42%. The ERG replicated the PSA using the company base case and achieved similar results.

5.1.2.3. Company's scenario analyses

The company conducted a number of scenario analyses to assess the impact of structural uncertainties and alternative settings and assumptions on the base case results. Scenario analysis results are provided in the CS (Document B, Table 56).

Reduced ICERs were reported when changing the data source of graft loss extrapolation to all imlifidase or 'unlikely to be transplanted' imlifidase patient groups, with ICERs of £29,253 and £29,556 respectively. Lower ICERs were also seen when reducing the annual discount rate of costs and outcomes and applying a caregiver disutility from Gray *et al.*[52]. All other scenarios saw an increase compared to the base case ICER, most notably when using the Li *et al.*[43] utility values an increase of 23% in the ICER was observed, and changing the data source for the overall survival extrapolation of those with a functioning graft from the all imlifidase patient group to the target population 'unlikely to be transplanted' group resulted in a considerably larger ICER of £46,896.

The scenario analyses presented were limited in number, with none exploring the impact of model selection on survival extrapolation, or the impact of an alternative dialysis overall survival approach. The scenario analysis results do however, highlight the influence of the utility source and data used to extrapolate for overall survival with a functioning graft upon the cost-effectiveness results.

5.2. Model validation and face validity check

The ERG found the company's cost-effectiveness model to be mostly free of errors with only minor issues identified in calculations (which moved the ICER by a maximum of 4.3%). Briefly, the errors corrected are listed below;

- Absence of first cycle transplant maintenance costs following the application of the half-cycle correction
    - To fix this the ERG applied the 0-6 month transplant maintenance costs in Cycle 1, with the seven to 12 month transplant maintenance costs applied in Cycle 2 and the one year-plus transplant maintenance costs applied for all subsequent years.
- AEs related to imlifidase and transplant not applied to all imlifidase patients following transplant
    - Due to the half-cycle correction applied in the model, although all patients in the imlifidase arm were administered imlifidase and received a transplant, the associated AEs did not get applied to 100% of patients in the imlifidase arm. The ERG correction applied imlifidase and transplant associated AEs to 100% of patients in the imlifidase arm
- Carer disutility not applied to Li *et al.* (2017)[43] utilities
    - The ERG correction applied a carer disutility to the patients receiving haemodialysis treatment. However, the Li *et al.* utility values are not used in the company's base case analysis therefore this correction results in no change to the company's base case ICER, only to this scenario analysis.

- Transplant AE costs for Cycle 4 are assigned to Cycle 5+:
    - The company have produced AE costs related to the cycle following transplant. From Cycle 5 onwards the cost applied per cycle should have been £749 however, the cost for Cycle 4 is applied in the company's base case (£1,076 per cycle).

The ERG corrected these minor errors resulting in a corrected company base case ICER of £31,971, an increase of £1,330 to the company submitted ICER (effect on the ICER presented in Table 17). Calculation errors were also identified for the calculation of the PSA results, detailed further in Section 5.1.2.2. However, the ERG note that the key problems associated with this appraisal are issues relating to conceptual aspects such as perspective and comparator, which are discussed in detail in Section 6.2.

Table 17: ERG corrections to the company base case

Preferred assumption	ICER when applied individually	Cumulative ICER £/QALY
Company base case	*30,641*	*30,641*
Apply 0-6 month transplant maintenance costs	*31,953*	*31,953*
Apply imlifidase and transplant AE's to all imlifidase	*30,683*	*31,994*
Apply caregiver disutility to Li *et al.* (2017)[43]*	*30,641*	*31,994*
Apply AE Cycle 5+ costs to transplant AEs	*30,618*	*31,971*
Company corrected base case	*31,971*	

Key: AE, adverse event; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Note: *the base case analysis does not use the Li et al. (2017) utility values, hence no difference is observed in the base case ICER when including this correction.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1. Data received from NHSBT

The population of interest in this appraisal, "those unlikely to receive a transplant under the existing protocols of the KOS", are a poorly defined group, with little information provided by the company on the outcomes and treatment patterns seen in NHS practice. For example, the split of dialysis modalities used in the economic model by the company was obtained from the whole waiting list population in the 21st annual UKRR report.[49]

To this end, the ERG requested data from NHSBT[53] to better inform the model. In order to operationalise the definition of "highly unlikely", the ERG requested data from NHSBT where patients were grouping by their degree of sensitisation; all patients, ≥85% CRF (referring to the traditional definition of highly sensitised), and ≥99% sensitised (reflecting a group of patients highly unlikely to match to any individual kidney). The ERG would like to place on record its thanks to NHSBT for their rapid and extremely helpful responses to our queries.

Though the patient group detailed by the company suggests immunological factors other than CRF are also likely to affect a patient's chance to receive a match, the ERG believed that in the absence of a full definition or alternative data source, the data provided by NHSBT[53] for the CRF ≥99% group provide a reasonable proxy to the population of interest for this appraisal. Furthermore, the ERG believed the data to relate more to the population of interest than the figures reported by the company from the 21st annual UKRR report.[49]

6.2. Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a number of additional exploratory and sensitivity analyses, which are summarised below:

- In order to explore an ITT population for the intervention arm, the ERG implemented an analysis where a proportion of patients received imlifidase but did not go on to achieve a negative crossmatch, and consequently, did not receive a transplant. This proportion was varied within the sensitivity analysis to explore the impact on the model results.
- The ERG analysis assumes that a proportion of highly-sensitised patients in the comparator arm will receive a transplant without imlifidase treatment. Data obtained from NHSBT[53] in the relevant patient population was used to populate this proportion, which was varied for sensitivity analysis.

- Data from NHSBT[53] revealed that not all patients on the transplant waiting list (in the whole population, and in the highly sensitised population) are receiving dialysis treatment. The ERG applied the distribution of dialysis status provided by NHSBT within the analysis for the patient group of interest. The ERG was also unable to validate the proportions for the types of dialysis used in the company base case therefore alternative proportions obtained from Table 2.6 of the UKRR 21st Annual Report[49] were applied in sensitivity analysis.
- The ERG considered a recently-published utility study by Cooper *et al.*[44] as a better proxy to inform the utility values in the cost-effectiveness model due to the methodological quality, but also year of searches (2020 vs 2006). The ERG implemented these values for the analysis, with values taken from Li *et al.*[43] explored in sensitivity analysis.
- The ERG applied an alternative caregiver disutility with better methodological validity to haemodialysis patients, and reduced the proportion of patients expected to have a caregiver to explore the impact on the model results.
- The ERG was concerned with the high cost assigned to haemodialysis travel by 'ambulance' in the company's analysis (>£200 for every 5th visit), and the effect on the ICER. The ERG considered an alternative approach by redistributing the proportion of patients from this transport to other NHS-cost incurring options.
- The ERG believed the omission of crossmatch tests following each full dose of imlifidase to be incorrect, and therefore have included the cost of crossmatch testing after every infusion of imlifidase.
- The average patient weight used by the company for the calculation of other drug costs (i.e. not imlifidase) was not taken from the clinical trials. The ERG has opted to implement the clinical trial average weight (i.e. the same as imlifidase) in order to more accurately reflect the patient population and be consistent in calculations.
- The ERG was concerned that the iBox predictive model was developed in a population with a different proportion of previous transplants compared to the population considered in the model. As previous transplant is a prognostic factor, the ERG has explored the impact of applying a relative risk to the iBox predictions.
- The ERG applied an increased cost for transplant to account for organ retrieval and transportation.

- The ERG considered that only a finite number of donor kidneys are available, and has therefore conducted a scenario analysis where the transplant is provided to patients who are not considered 'highly-sensitised' and thus, do not require imlifidase treatment.
- The ERG was concerned that DSA testing costs have not been captured in the model, therefore an analysis is conducted where DSA tests are applied once annually as transplant maintenance and at the time of graft loss.

6.3. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The analyses described in Section 6.2 are described in turn within each section below. The impact on the ICER described below refers to the company's base case ICER including the ERG corrections detailed in Section 5.2.

6.3.1. Patients receiving imlifidase but unable to progress to transplant

As discussed in Section 4.2.4 and Section 3.2.4, while imlifidase appears to be efficacious, there is uncertainty in the rate of crossmatch conversion from positive to negative. Although the rate is clearly high, one patient failed to achieve a negative FACS crossmatch (and received a transplant regardless as a negative virtual crossmatch result was achieved and clinical judgement supported the proceedure), with two further patients having adverse reactions to imlifidase and were unable to receive a full dose (and subsequent transplant). As such the ERG has adapted the company's model to allow a proportion of patients to receive imlifidase but not to undergo transplantation. As the true rate of crossmatch conversion is unknown the ERG has adjusted the proportion to receive transplant in the intervention arm by accounting for the patients who did not receive the full dose. Furthermore, in a scenario analysis, this proportion is also adjusted to account for the patient who did not achieve a negative FACS crossmatch. This resulted in a rate of transplant for the imlifidase arm of 96.3% in the ERG base case and 94.4% in a scenario analysis as opposed to the 100% in the company submission. This is consistent with the clinical findings where the high rate of crossmatch conversion was also subject to uncertainty.

Decreasing the proportion of imlifidase patients to receive a transplant from 100% to 96.3% resulted in an increase of £2,488 to the ICER (£31,971 to £34,459). Alternative proportions including the scenario to account for the failed conversion to a negative FACS crossmatch are explored in scenario analysis in Section 6.4.1.1.

6.3.2. Likelihood of receiving transplant without imlifidase

The economic model submitted by the company does not allow for any patients on dialysis to receive a transplant at any point in their lifetime. The ERG highlights concern with this approach in Section 4.2.4. In order to reflect that some (though not all) highly sensitised dialysis patients would receive a transplant without treatment with imlifidase, the ERG conducted the following additional analyses:

- Inclusion of an additional ERG comparator ('dialysis and transplant') where a proportion of dialysis patients receive a transplant.
- Heatmap combining the assumed proportion of dialysis patients to receive a transplant and the assumed proportion of imlifidase patients to receive a transplant.

The ERG noted that the 'dialysis and transplant' comparator only provides a limited comparison between the treatment arms as, due to the model coding, patients were assigned to either dialysis or transplant at Cycle 0. In practice it is expected that patients are likely to remain on dialysis prior to a suitable transplant becoming available – however, as patients cannot transition from dialysis to transplant in the model, no dialysis costs can be accrued prior to transplant to reflect the expected delay in receiving a transplant.

With this limitation in mind the ERG was able to perform the comparison using data provided by NHSBT[9] for years 2015 to 2019. The data showed that 119 transplants occurred for the ≥99% cRF group in the year 2019/2020 (the first full year of the revised KOS), with a mean of 77 transplants performed in the same patient group over the previous four years (2015/2016 - 2018/2019). As of 30 September 2020, there were 495 highly-sensitised patients with a cRF of ≥99% on the transplant waiting list. The 119 patients who received a transplant in the 2019/2020 year corresponds to 24.0% of 495 patients on the waiting list.

In reality, the ERG expects the number of transplants received in the 2019/2020 year to likely be inflated due to a backlog of highly sensitised patients who were suddenly assigned a higher weighting in 2019 as a result of the revised KOS. As such, the mean number of transplants over years 2015 to 2019 (85) was used to calculate an expected proportion of highly sensitised dialysis patients who would receive a transplant without treatment with imlifidase. This provided an annual probability of 17.2% (85/495). Due to the confines of the model structure, it was assumed that patients would remain fit enough for transplant for two years from model entry, following which they would become ineligible in keeping with clinical input to the ERG that

eventually patients would become too sick to be transplanted. This provided a proportion of 31.4% of patients who could expect to receive a transplant in the comparator arm.

The ERG noted that due to the limitations of the model, the patients who undergo transplant in the comparator arm would incur slightly different costs in reality, as the rate of transplant would be effectively spread over time, as opposed to all occurring at Cycle 0 in the model. This unfortunately is a limitation of the model coding, but is not expected to radically change the results and represents, along with the duration for which patients may be able to undergo a transplant, a limitation.

Furthermore, clinical opinion to the ERG indicated that DSA monitoring is likely to be more frequent for patients who undergo an HLA incompatible transplant. Therefore, the ERG has applied DSA costs; monthly for the first 6 months, once every two months for 7-12 months and once annually thereafter following transplant for the patients receiving a transplant without imlifidase treatment. DSA costs are further discussed in Section 6.3.12.

Allowing 31.44% of dialysis patients to receive a transplant resulted in an ICER change from £31,971 to £59,335.

6.3.3. Changing the comparator to established clinical management, from dialysis

As discussed in Section 4.2.4, the company's economic model assumed all non-transplant patients receive dialysis. However, data provided by NHSBT[9] in the highly sensitised group (≥99%), showed that some patients are not currently on any dialysis treatment (77/491, 15.7%), with the remainder receiving haemodialysis (366/491, 74.5%) and peritoneal dialysis (48/491, 9.8%). Clinical input to the ERG agreed with this finding, with the explanation that a proportion of patients are listed for transplant pre-emptively – i.e. when eGFR <15 but still with enough kidney function to not require dialysis, whilst other patients are those with failing grafts who again maintain sufficient kidney function to be dialysis free, but do require transplantation (i.e. relisting).

To reflect the NHSBT data, the ERG implemented the proportions of patients to receive each dialysis modality (including no dialysis) in their base case analysis as taken from the NHSBT data. The ERG understand it is likely that all patients may receive dialysis at some point however, particularly as patients age. It is therefore assumed that after the first two years, all patients will move to dialysis in the ratio seen in the NHSBT data. The ERG acknowledges this

assumption (i.e. a maximum two years without dialysis) to be a limitation of the analysis however believe in the absence of data, it represents a plausible value, which can be changed based on data or expert opinion should the committee wish.

A further limitation is that as there is a lack of available data to inform overall survival for the patients not on dialysis, overall survival was assumed to follow the same trajectory as those on dialysis in the model. This assumption may result in an underestimate of the effectiveness of the comparator arm as it is likely these patients are healthier than those who are on dialysis i.e. they are earlier in the disease pathway.

Changing the comparator to reflect established clinical management represented an increase in the ICER from £31,971 to £40,999.

6.3.4. Utility values used for patients in the model

Using data from the recently published meta-analysis from Cooper *et al.,*[44] and assuming 25% of patients are aged over 65 years (in line with the clinical studies), the ERG calculated that using longitudinal estimates, pre-transplant patients had a mean utility of 0.7385, which increased to 0.84 a year after transplant (the timepoint measured in the studies). For simplicity these values were used pre-/post-transplant, with age adjustments then applied throughout the model time horizon using the decrements from Table A of Kind *et al.*[46]

Using Cooper *et al.*[44] as the utility source resulted in an increase of £6,701 to the ICER (£31,971 to £38,672).

6.3.5. Utility values used for carers in the model

As discussed in Section 4.2.7, a carer disutility of 0.03 was applied for patients in receipt of haemodialysis. The ERG anticipated that not all haemodialysis patients would have a caregiver and so applied a caregiver utility to 90% of haemodialysis patients (rather than 100% in the company's base case), with 100% of patients explored as a scenario analysis.

Incorporating a 0.03 utility decrement to account for caregivers of haemodialysis patients results in a reduction of £541 (£31,971 to £31,431). Reducing the proportion of patients with a caregiver from 100% to 90% resulted in an increase of £38 to the ICER (£31,971 to £32,009)' to put them separately.

6.3.6. Cost of patient transport

The cost of patient ambulance transport used by the company (£219) is extremely similar to that of an emergency in NHS reference costs 2018-2019[54] (ASS02 See and treat and convey, £257), and is in reality likely to be a (shared) community ambulance. Furthermore, it is not clear other costs (such as taxis) need inflating given changes in the transport market over time to make it more competitive (such as the increase in ride hailing apps, and changes in transport patterns) – with 10 years since the data used was collected.

Due to this uncertainty and the absence of suitable costs, the has ERG redistributed the 18% from ambulance to the other NHS-incurred travel costs. Table 21 presents the proportion of haemodialysis patients assigned each mode of transport in the company analysis, and the reweighted proportions preferred by the ERG.

Table 18: Comparison of haemodialysis transport in company and ERG analyses

Transport	Company	ERG
Ambulance service vehicle	18%	0%
Hospital provided car	12%	16.7%
Hospital arranged taxi	12%	16.7%
Hospital transport vehicle	22%	30.6%
Public or private transport	36%	36%

Abreviations: ERG, Evidence Review Group

Applying the ERG's reweighted proportions saw an increase of £5,114 to the ICER (£31,971 to £37,085). The ERG note however that this input is subject to substantial uncertainty, and further data could provide a better understanding of the true costs to the NHS of patient transport.

6.3.7. Cost of crossmatch tests

The company does not apply any costs associated with crossmatch testing in the model. The ERG has discussed concerns with this approach in Section 4.2.8.1.

In order to capture the costs of crossmatch testing for the analysis, the ERG applied a cost of £300 following each full dose of imlifidase received. The ERG was unable to find the cost of one FACS crossmatch test (FACS crossmatch tests were used in the clinical studies) alone however, the cost of one FACS test with one CDC test was reported in the literature[51] and so, to account for just one test being used, the ERG has halved this cost and implemented this in the model.

Applying crossmatch test costs within the model results in an increase of £78 to the ICER (31,971 to £32,049), though further information would be able to resolve this uncertainty.

6.3.8. Patient weight

The ERG found the company to have taken the average patient weight of 75 kg applied in the model from a Welsh study in 2009.[55] The ERG found the average weight of patients in the 'all imlifidase' patient group to be 69 kg and so have applied this in a sensitivity analysis for consistency with the costing of imlifidase (which uses actual patient weights). Using the average patient weight from the clinical studies resulted in an increase of £29 to the ICER (£31,971 to £31,942).

6.3.9. Survival post transplant in a highly pre-treated patient population

The ERG noted that the patient population in the highly sensitised group will potentially have worse outcomes than a 'standard' transplant population for four reasons:

- The increased CIT *ceteris paribus* when imlifidase is required to enable a transplant;
- The presence of antibodies against the donor kidney;
- The increased length of time these patients will likely have spent on dialysis;
- The number of patients who have had a prior transplant, compared to the iBox population on which estimates were based (and in which no coefficient is described for prior transplant).

Although it was not possible to quantify these concerns, the ERG provided a sensitivity analysis where a hazard ratio of 0.95 is applied to the post-transplant survival, to understand the importance of long-term survival. This change increased the ICER by £1,426 (£31,971 to £33,397)

6.3.10. Transplant costing

According to the NHSBT Activity report 2019/20[56] there were 3,760 organ transplants in the UK with a net expenditure of NHSBT of £79.9 million[4], which gives a crude cost per organ of £21,010. As the organ for any transplant has to be provided – including managing donor lists, liasing with families, retreiving organs, and transporting them under tight time windows, these costs should be included within the appraisal to be consistent with the NICE methods guide (the

inclusion of all relevant costs and benefits). As such the ERG presented a scenario including this cost for transplant.

It should be noted that this cost is applied for any transplant (including in the comparator arm). The ERG acknowledged it is also likely that the cost per organ is not likely to be the same for all organs and donor types; as such improved estimates of cost may be helpful, if available. Including this cost increased the ICER from £31,971 to £33,583.

6.3.11. Reflecting the opportunity cost of a donor kidney

As discussed in both the CS and ERG report, donor kidneys are scarce with the waiting list evidencing that demand exceeds supply. As with the principle of cost-effectiveness where money not spent on an intervention will be spent elsewhere in the system, any kidneys not received by imlifidase patients would be received by other patients; i.e. imlifidase will not increase the number of kidneys available to transplant.

This question is one of the scope of the appraisal, and a question which is not covered by the NICE scope, or anticipated by the NICE methods guide (though the reflection of all costs and benefits might indicate that the opportunity [health] cost of the kidney be included).

In order to explore the impact of this opportunity cost, a comparison was made by the ERG of giving a kidney to an imlifidase patient vs to a patient not requiring imlifidase (who may or may not be in the >99% sensitised group). Although limited in its application, this scenario showed the use of imlifidase to be dominated; using a threshold of £30,000 per QALY the ERG found a net benefit of [redacted] / net health benefit of [redacted] QALYs.

6.3.12. DSA testing

As discussed in Section 4.2.8.5, no costs associated with DSA testing are applied within the model. Clinical advice to the ERG indicated that in HLA-incompatible transplants DSA monitoring would indeed be administered more frequently than with an HLA-compatible transplant. As imlifidase induces a negative crossmatch by depleting the antibodies, an HLA-compatible transplant can be performed. Although these antibodies are likely to rebound following transplant, clinical advice to the ERG was conflicting on whether additional DSA monitoring would be required for this population following imlifidase. The ERG was also unable to interpret the clinical outcome of HLA rebounds due to limited reporting in the CS (Section 3.2.4), which provided further uncertainty on the monitoring of DSAs post-transplant.

Clinical opinion was, however, in agreement that DSA testing would be implemented (as a minimum) when a graft failure is suspected. At clarification stage the company provided the cost for a DSA test on one antigen (£55) and stated clinical opinion was that three antigens of interest could be expected however, this could be between one and six antigens. The ERG explored the effect on the model results when including DSA tests for use in transplant maintenance (tested for three antigens, once annually) and at the time of graft failure. Therefore, the ERG applied the cost for three antigens (£155) at the time of graft failure as a scenario analysis in the model. DSA test costs are also applied in the ERG's base case for the comparator patients who go on to receive a transplant, further discussed in Section 6.3.2.

The inclusion of these costs resulted in an increase of £373 in the ICER from £31,971 to £32,344. The ERG noted, however, that it appears clinicians may perform more DSA testing than this, which represents an uncertainty about how imlifidase would be used in practice, and may be worthy of consensus being gained, and then implemented in modelling.

6.3.13. Overview results of exploratory and sensitivity analyses

An overview results of exploratory and sensitivity analyses is provided in Table 19.

Table 19: Exploratory and sensitivity analyses

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's base case	[redacted]	[redacted]	*£30,641*
ERG error fixes			
Apply 0-6 month transplant maintenance costs	[redacted]	[redacted]	*£31,953*
Apply imlifidase and transplant AE's to all imlifidase	[redacted]	[redacted]	*£30,683*
Apply caregiver disutility to Li *et al.* (2017)[43]*	[redacted]	[redacted]	*£30,641*
Apply AE Cycle 5+ costs to transplant AEs	[redacted]	[redacted]	*£30,618*
Company corrected base case	[redacted]	[redacted]	*£31,971*
Scenarios below include the four ERG error fixes above			
Reduce the proportion of imlifidase patients to receive transplant – 96.3%	[redacted]	[redacted]	*£34,459*

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Allow a proportion of dialysis patients to receive a transplant – 31.44%	[redacted]	[redacted]	*£59,335*
Apply NHSBT proportion of dialysis modality (including not on dialysis)	[redacted]	[redacted]	*£40,999*
Utility source – Cooper *et al.* (2020)[44]	[redacted]	[redacted]	*£38,672*
Caregiver disutility source – Thomas *et al.* (2015)[45]	[redacted]	[redacted]	*£31,431*
Reduce the proportion of HD patients with a caregiver to 90%	[redacted]	[redacted]	*£32,009*
Redistribute hospital-paid dialysis travel cost	[redacted]	[redacted]	*£37,085*
Apply crossmatch test cost per imlifidase dose	[redacted]	[redacted]	*£32,049*
Change average patient weight to 69 kg	[redacted]	[redacted]	*£31,942*
Apply HR to iBox graft estimates – 0.95*	[redacted]	[redacted]	*£33,397*
Apply alternative transplant cost - £21,000*	[redacted]	[redacted]	*£33,583*
Change comparator to 'Non-sensitised transplant'*	[redacted]	[redacted]	*Dominated*
Include DSA test costs	[redacted]	[redacted]	*£32,344*
ERG base case	[redacted]	[redacted]	*£98,496*

Abbreviations: AE, Adverse event; DSA, donor-specific antibodies; ERG, Evidence Review Group; HD, haemodialysis; HR, Hazard Ratio; ICER, incremental cost-effectiveness ratio; kg, kilogram; NHSBT, National Health Service Blood and Transplant; QALY, quality-adjusted life year

Note:

*the base case analysis does not use the Li et al. (2017) utility values, hence no difference is observed in the base case ICER when including this correction

* Not included in the ERG base case

6.4. ERG's preferred assumptions

The ERG's preferred base-case analysis comprises several alternative model settings and assumptions:

1. Application of 96.3% of patients administered imlifidase to receive a subsequent transplant compared to 100% in the company's base case (Section 6.3.1).

2. Allow 31.44% of dialysis patients to receive a transplant compared to 0% in the company's base case (Section 6.3.2).
3. Application of the dialysis status distribution reported by NHSBT. Most notably this allows a proportion of patients in the comparator arm to receive no dialysis (Section 6.3.3).
4. Implement utility values taken from Cooper *et al.*[44] (Section 6.3.4).
5. Implement caregiver disutility from Thomas *et al.*[45] (Section 6.3.5).
6. Apply caregiver disutility to 90% of haemodialysis patients compared to 100% in the company's base case (Section 6.3.5).
7. Redistribute the distribution of hospital-paid transport to exclude 'ambulance' (Section 6.3.6).
8. Include the cost of one crossmatch test following each full dose of imlifidase (Section 6.3.7).
9. Use the average patient weight obtained from the clinical trials throughout the model (Section 6.3.8).
10. Include the cost of DSA test (three antigens) annually for transplant patients and at time of graft loss (Section 6.3.12).

6.4.1. Summary of ERG's base case settings and assumptions

Despite the limitations highlighted within the company's model, the ERG determined a set of preferred settings and assumptions that are believed to represent a more plausible estimate of the cost-effectiveness of imlifidase. However, the ERG emphasised that several preferred assumptions such as the proportion of dialysis patients who were likely to receive a transplant without imlifidase and the amount of time comparator patients spend receiving no dialysis remain uncertain due to either model or knowledge limitations.

The ERG's preferred model settings and assumptions are summarised in Table 20. The individual and cumulative impact of each setting on the estimated ICER is presented alongside each change. The results presented are aligned with the base case results provided by the company, including equivalent settings.

Table 20: ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Individual change to corrected ICER £/QALY	Cumulative ICER £/QALY
Company base case	*Section 5.1.1*	-	*30,641*
Company base case following ERG corrections	*Section 5.2*	-	*31,971*
Reduce the proportion of imlifidase patients to receive transplant – 96.3%	*Section 6.3.1*	*34,459*	*34,459*
Allow a proportion of dialysis patients to receive a transplant – 31.44%	*Section 6.3.2*	*59,335*	*64,592*
Apply NHSBT proportion of dialysis modality (including not on dialysis)	*Section 6.3.3*	*40,999*	*73,595*
Utility source – Cooper *et al.* (2020)[44]	*Section 6.3.4*	*38,672*	*89,315*
Caregiver disutility source – Thomas *et al.* (2015)[45]	*Section 6.3.5*	*31,431*	*90,647*
Reduce the proportion of HD patients with a caregiver to 90%	*Section 6.3.5*	*32,009*	*90,418*
Redistribute hospital-paid dialysis travel cost	*Section 6.3.6*	*37,085*	*94,562*
Apply crossmatch test cost per imlifidase dose	*Section 6.3.7*	*32,049*	*94,710*
Change average patient weight to 69 kg	*Section 6.3.8*	*31,942*	*94,674*
Include DSA test costs	*Section 6.3.12*	*32,344*	*95,131*

Abbreviations: DSA, donor-specific antibodies; ERG, Evidence Review Group; HD, haemodialysis; ICER, incremental cost-effectiveness ratio; kg, kilogram; NHSBT, National Health Service Blood and Transplant; QALY, quality adjusted life year.

A comparison of the company's base case analysis and the ERG's preferred analysis results are presented in Table 21. The equivalent results of PSA using the ERG preferred assumptions are also provided.

Table 21: Comparison of company and ERG results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*30,641*
ERG base case (deterministic)							

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*95,131*
Company base case (probabilistic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*31,948*
ERG base case (probabilistic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*97,728*

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year

Note: It was not possible to obtain LY results from the cost-effectiveness model

6.4.1.1. ERG scenario analyses

A comparison of the company's scenario analyses using the ERG's preferred assumptions versus the company's base case is provided in Table 22.

Table 22: Comparison of company and ERG scenario analysis results

Scenario	ICER (£/QALY)	
	Company	ERG
Base-case	*30,641*	*95,131*
Company scenario analyses		
Annual discount rate (costs and outcomes) - 1.5%	*22,163*	*70,373*
Time horizon – 10 years	*62,857*	*225,779*
Time horizon – 20 years	*35,676*	*120,898*
Utility source – Li *et al.* (2017)[43]	*37,612*	*97,883*
Graft loss extrapolation – All imlifidase patients	*29,253*	*92,919*
Graft loss extrapolation – 'Unlikely to be transplanted' patients	*29,556*	*93,551*
OS with a functioning graft – 'Unlikely to be transplanted' patients	*46,896*	*206,409*
No caregiver disutility	*31,012*	*93,021*
Caregiver disutility source – Gray *et al.* (2019)[52]	*29,036*	*98,035*
ERG scenario analyses		
Account for 51/52 patients achieving a negative FACS crossmatch (proportion of imlifidase patient to receive a transplant – 94.4%)	*34,442*	*98,696*
Proportion of imlifidase patients to receive a transplant – 90%	*37,821*	*108,171*

Scenario	ICER (£/QALY)	
	Company	ERG
Proportion of imlifidase patients to receive a transplant – 99%	*31,294*	*90,277*
Proportion of dialysis patients to receive a transplant – 5%	*33,727*	*61,975*
Proportion of dialysis patients to receive a transplant – 10%	*37,269*	*66,687*
Proportion of dialysis patients to receive a transplant – 20%	*45,681*	*77,965*
Use UKRR distribution of dialysis modalities	*33,771*	*89,966*
Proportion of haemodialysis patients with a caregiver – 100%	*30,641*	*95,371*
Apply HR to iBox graft estimates – 0.90	*33,605*	*101,217*
Apply HR to iBox graft estimates – 0.95	*32,036*	*97,997*
Apply alternative transplant cost - £21,000	*32,354*	*97,217*
Change comparator to 'Non-sensitised transplant'	*Dominated*	*Dominated*
Change OS dialysis source – ERA-EDTA	*33,819*	*86,005*

Key: ERA-EDTA, European Renal Association – European Dialysis Transplant Association; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life-year;

Figure 3 presents a heat map showing the effect on the company's base case ICER (without ERG correction) when the proportion of patients to receive a transplant in the intervention and comparator arms is varied. The company's base case, 100% imlifidase patients to receive transplant, 0% comparator to receive transplant, is highlighted on the figure.

Figure 3: Heat map of the company's base case assumptions varied by the proportion to receive transplant in each arm

Proportion of dialysis patients who receive a transplant	*Proportion of imlifidase patients who receive a transplant*										
	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%
0%	31k	31k	32k	33k	33k	34k	35k	35k	36k	37k	38k
1%	31k	32k	32k	33k	34k	35k	35k	36k	37k	38k	38k
2%	32k	32k	33k	34k	35k	35k	36k	37k	38k	38k	39k
3%	32k	33k	34k	35k	35k	36k	37k	38k	38k	39k	40k
4%	33k	34k	34k	35k	36k	37k	38k	38k	39k	40k	41k
5%	34k	34k	35k	36k	37k	37k	38k	39k	40k	41k	42k
6%	34k	35k	36k	37k	37k	38k	39k	40k	41k	42k	43k
7%	35k	36k	37k	37k	38k	39k	40k	41k	42k	42k	43k
8%	36k	37k	37k	38k	39k	40k	41k	42k	42k	43k	44k
9%	37k	37k	38k	39k	40k	41k	42k	42k	43k	44k	45k
10%	37k	38k	39k	40k	41k	41k	42k	43k	44k	45k	46k
11%	38k	39k	40k	41k	41k	42k	43k	44k	45k	46k	47k
12%	39k	40k	40k	41k	42k	43k	44k	45k	46k	47k	48k
13%	40k	40k	41k	42k	43k	44k	45k	46k	47k	48k	49k
14%	40k	41k	42k	43k	44k	45k	46k	47k	48k	49k	50k
15%	41k	42k	43k	44k	45k	46k	47k	48k	49k	50k	51k
16%	42k	43k	44k	45k	46k	47k	48k	49k	50k	51k	52k
17%	43k	44k	45k	46k	47k	48k	49k	50k	51k	52k	53k
18%	44k	45k	46k	47k	48k	49k	50k	51k	52k	53k	55k
19%	45k	46k	47k	48k	49k	50k	51k	52k	53k	55k	56k
20%	46k	47k	48k	49k	50k	51k	52k	53k	55k	56k	57k
21%	47k	48k	49k	50k	51k	52k	53k	54k	56k	57k	58k
22%	48k	49k	50k	51k	52k	53k	54k	56k	57k	58k	60k
23%	49k	50k	51k	52k	53k	54k	56k	57k	58k	60k	61k
24%	50k	51k	52k	53k	54k	56k	57k	58k	60k	61k	62k
25%	51k	52k	53k	54k	56k	57k	58k	59k	61k	62k	64k
26%	52k	53k	54k	55k	57k	58k	59k	61k	62k	64k	65k
27%	53k	54k	55k	57k	58k	59k	61k	62k	64k	65k	67k
28%	54k	55k	57k	58k	59k	61k	62k	64k	65k	67k	68k
29%	55k	57k	58k	59k	61k	62k	64k	65k	67k	68k	70k
30%	56k	58k	59k	61k	62k	63k	65k	67k	68k	70k	72k
31%	58k	59k	60k	62k	63k	65k	66k	68k	70k	72k	73k
32%	59k	60k	62k	63k	65k	66k	68k	70k	71k	73k	75k
33%	60k	62k	63k	65k	66k	68k	70k	71k	73k	75k	77k
34%	62k	63k	65k	66k	68k	70k	71k	73k	75k	77k	79k
35%	63k	65k	66k	68k	70k	71k	73k	75k	77k	79k	81k

Figure 4 presents a heat map showing the effect on the company's base case ICER with ERG correction when the proportion of patients to receive a transplant in the intervention and comparator arms is varied. The company's base case, 100% imlifidase patients to receive transplant, 0% comparator to receive transplant, is highlighted on the figure.

Figure 4: Heat map of the company's ERG corrected base case assumptions varied by the proportion to receive transplant in each arm

Proportion of dialysis patients who receive a transplant	*Proportion of imlifidase patients who receive a transplant*										
	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%
0%	32k	32k	33k	34k	34k	35k	36k	36k	37k	38k	39k
1%	32k	33k	34k	34k	35k	36k	36k	37k	38k	39k	40k
2%	33k	34k	34k	35k	36k	36k	37k	38k	39k	40k	40k
3%	34k	34k	35k	36k	36k	37k	38k	39k	39k	40k	41k
4%	34k	35k	36k	36k	37k	38k	39k	39k	40k	41k	42k
5%	35k	36k	36k	37k	38k	39k	39k	40k	41k	42k	43k
6%	35k	36k	37k	38k	39k	39k	40k	41k	42k	43k	44k
7%	36k	37k	38k	38k	39k	40k	41k	42k	43k	44k	44k
8%	37k	38k	38k	39k	40k	41k	42k	43k	44k	44k	45k
9%	38k	38k	39k	40k	41k	42k	43k	43k	44k	45k	46k
10%	38k	39k	40k	41k	42k	43k	43k	44k	45k	46k	47k
11%	39k	40k	41k	42k	42k	43k	44k	45k	46k	47k	48k
12%	40k	41k	42k	42k	43k	44k	45k	46k	47k	48k	49k
13%	41k	42k	42k	43k	44k	45k	46k	47k	48k	49k	50k
14%	41k	42k	43k	44k	45k	46k	47k	48k	49k	50k	51k
15%	42k	43k	44k	45k	46k	47k	48k	49k	50k	51k	52k
16%	43k	44k	45k	46k	47k	48k	49k	50k	51k	52k	53k
17%	44k	45k	46k	47k	48k	49k	50k	51k	52k	53k	55k
18%	45k	46k	47k	48k	49k	50k	51k	52k	53k	54k	56k
19%	46k	47k	48k	49k	50k	51k	52k	53k	54k	56k	57k
20%	47k	48k	49k	50k	51k	52k	53k	54k	56k	57k	58k
21%	48k	49k	50k	51k	52k	53k	54k	56k	57k	58k	59k
22%	49k	50k	51k	52k	53k	54k	55k	57k	58k	59k	61k
23%	50k	51k	52k	53k	54k	55k	57k	58k	59k	61k	62k
24%	51k	52k	53k	54k	55k	57k	58k	59k	61k	62k	63k
25%	52k	53k	54k	55k	57k	58k	59k	60k	62k	63k	65k
26%	53k	54k	55k	56k	58k	59k	60k	62k	63k	65k	66k
27%	54k	55k	56k	58k	59k	60k	62k	63k	65k	66k	68k
28%	55k	56k	58k	59k	60k	62k	63k	65k	66k	68k	69k
29%	56k	58k	59k	60k	62k	63k	65k	66k	68k	69k	71k
30%	58k	59k	60k	62k	63k	64k	66k	68k	69k	71k	73k
31%	59k	60k	62k	63k	64k	66k	67k	69k	71k	72k	74k
32%	60k	61k	63k	64k	66k	67k	69k	71k	72k	74k	76k
33%	61k	63k	64k	66k	67k	69k	71k	72k	74k	76k	78k
34%	63k	64k	66k	67k	69k	71k	72k	74k	76k	78k	80k
35%	64k	66k	67k	69k	71k	72k	74k	76k	78k	80k	82k

Figure 5 presents a heat map showing the effect on the ERG's base case when the proportion of patients to receive a transplant in the intervention and comparator arms is varied. The company's base case, 96.3% imlifidase patients to receive transplant, 31.4% comparator to receive transplant, is highlighted on the figure.

Figure 5: Heat map of the ERG's base case assumptions varied by the proportion to receive transplant in each arm

Proportion of dialysis patients who receive a transplant	Proportion of imlifidase patients who receive a transplant										
	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%
0%	55k	56k	56k	57k	58k	59k	60k	61k	62k	63k	64k
1%	56k	56k	57k	58k	59k	60k	61k	62k	63k	64k	65k
2%	56k	57k	58k	59k	60k	61k	62k	63k	64k	65k	66k
3%	57k	58k	59k	60k	61k	62k	63k	64k	65k	66k	67k
4%	58k	59k	60k	61k	62k	62k	63k	64k	66k	67k	68k
5%	59k	60k	61k	61k	62k	63k	64k	65k	66k	68k	69k
6%	60k	60k	61k	62k	63k	64k	65k	66k	67k	69k	70k
7%	60k	61k	62k	63k	64k	65k	66k	67k	69k	70k	71k
8%	61k	62k	63k	64k	65k	66k	67k	68k	70k	71k	72k
9%	62k	63k	64k	65k	66k	67k	68k	69k	71k	72k	73k
10%	63k	64k	65k	66k	67k	68k	69k	71k	72k	73k	74k
11%	64k	65k	66k	67k	68k	69k	70k	72k	73k	74k	75k
12%	65k	66k	67k	68k	69k	70k	72k	73k	74k	75k	77k
13%	66k	67k	68k	69k	70k	71k	73k	74k	75k	76k	78k
14%	67k	68k	69k	70k	71k	73k	74k	75k	76k	78k	79k
15%	68k	69k	70k	71k	73k	74k	75k	76k	78k	79k	80k
16%	69k	70k	71k	72k	74k	75k	76k	78k	79k	80k	82k
17%	70k	71k	72k	74k	75k	76k	77k	79k	80k	82k	83k
18%	71k	72k	73k	75k	76k	77k	79k	80k	82k	83k	85k
19%	72k	73k	75k	76k	77k	79k	80k	81k	83k	84k	86k
20%	73k	75k	76k	77k	79k	80k	81k	83k	84k	86k	88k
21%	75k	76k	77k	78k	80k	81k	83k	84k	86k	87k	89k
22%	76k	77k	78k	80k	81k	83k	84k	86k	87k	89k	91k
23%	77k	78k	80k	81k	83k	84k	86k	87k	89k	91k	92k
24%	78k	80k	81k	83k	84k	86k	87k	89k	90k	92k	94k
25%	80k	81k	82k	84k	85k	87k	89k	90k	92k	94k	96k
26%	81k	82k	84k	85k	87k	89k	90k	92k	94k	96k	98k
27%	82k	84k	85k	87k	89k	90k	92k	94k	96k	97k	99k
28%	84k	85k	87k	88k	90k	92k	94k	95k	97k	99k	101k
29%	85k	87k	88k	90k	92k	94k	95k	97k	99k	101k	103k
30%	87k	88k	90k	92k	93k	95k	97k	99k	101k	103k	105k
31%	88k	90k	92k	93k	95k	97k	99k	101k	103k	105k	107k
32%	90k	91k	93k	95k	97k	99k	101k	103k	105k	107k	110k
33%	91k	93k	95k	97k	99k	101k	103k	105k	107k	110k	112k
34%	93k	95k	97k	99k	101k	103k	105k	107k	109k	112k	114k
35%	95k	97k	99k	101k	103k	105k	107k	109k	112k	114k	117k

6.5. Conclusions of the cost-effectiveness section

The work performed by the ERG addresses several shortcomings in the company submission. Although the model calculations were mostly accurate (with corrections having small influences on the ICER), the model omitted to include the appropriate application of the intervention (via an ITT approach) and the appropriate comparator. Other changes to parameters included using appropriate quality of life data, and accounting for missing costs.

Although the ERG's base case ICER increased substantially, this was almost entirely due to reflecting the decision problem, reflecting that not all imlifidase patients achieve transplant and

not all standard care patients fail to achieve transplant. The other change which substantially affects the results is reflecting the distribution of dialysis (and no dialysis) received by patients in practice, versus the split of dialysis only (taken from a general population). For completeness, changing only these three items increased the ICER from the company's base case of £30,641 to £72,593; with correcting costing and other issues (such as utilities) accounting for the remaining increase to £95,131 which represents the ERG's base case.

The findings of sensitivity and scenario analysis further demonstrated the importance of understanding the opportunity cost of kidneys (which leads to imlifidase being dominated, a loss of [redacted] QALYs to the health care system using a £30,000 threshold and the company's uncorrected assumptions). Other important factors included the survival of patients (which the ERG was unable to adequately assess given the data used), and utility values used (which are uncertain due to being taken from the literature, and not the specific population).

The remaining issue the ERG noted was the structural uncertainty present in the model. Although the company model with the ERG base case represents a reasonable estimation given the information available, there exists uncertainty in how imlifidase would be used in practice, what the survival of patients would look like, and their quality of life (as no data was captured in the clinical trial). Although not able to be included in the model, these are uncertainties that the ERG would highlight.

7. END OF LIFE

The CS contains no mention of imlifidase in terms of an end of life treatment. The ERG agreed that given the average life expectancy in this population is notably longer than two years, NICE's end-of-life considerations are not applicable to this appraisal and are therefore not discussed further.

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Appendix A: Transplanted population

Pooled baseline trial characteristics from transplant patients were provided by the company (n=46) CS, Appendix C, Table 36, p.97 [EPAR]).

Table 23: Demographics and baseline characteristics of transplanted patients

Characteristics	Study 02 N=1	Study 03 N=10	Study 04 N=17	Study 06 N=18	All N=46
Age (years)	N (%)	N (%)	N (%)	N (%)	N (%)
>35 yrs	0 (0)	2 (20)	6 (35)	5 (28)	13 (28)
35-49	0 (0)	1 (10)	5 (30)	11 (61)	17 (37)
50-64	1 (100)	5 (50)	6 (35)	2 (11)	14 (31)
>64	0 (0)	2 (20)	0 (0)	6 (6)	2 (4)
Sex	N (%)	N (%)	N (%)	N (%)	N (%)
Male	1 (100)	3 (30)	8 (47)	13 (72)	25 (54)
Female	0 (0)	7 (70)	9 (53)	5 (28)	21 (46)
Race	N (%)	N (%)	N (%)	N (%)	N (%)
Caucasian	1 (100)	9 (90)	14 (82)	11 (61)	35 (76)
Asian	0 (0)	1 (10)	2 (12)	1 (6)	4 (9)
Black	0 (0)	0 (0)	0 (0)	4 (22)	4 (9)
Other	0 (0)	0 (0)	1 (6)	2 (11)	3 (6)
Historical transplantations (n)	N (%)	N (%)	N (%)	N (%)	N (%)
0					
1	0 (0)	6 (60)	6 (35)	2 (11)	14 (31)
2	1 (100)	4 (40)	9 (53)	9 (50)	22 (48)
3	0 (0)	0 (0)	2 (12)	5 (28)	8 (17)
	0 (0)	0 (0)	0 (0)	2 (11)	2 (4)
Total time of dialysis (years)					
Mean SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	2.5	2.1	5.4	5.3	4.9
cPRA (%) MFI cut-off >2000)					
Median	42	71.8	98.6	99.6	98.4
No of previous transplants					

Characteristics	Study 02 N=1	Study 03 N=10	Study 04 N=17	Study 06 N=18	All N=46
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Living donor	0	2	0	5	7
Deceased donor	1	8	17	13	39
Previous attempts of desensitisation (n)	0	0	14	5	19

Abbreviations: cPRA, calculated panel-reactive antibodies; MFI, mean fluorescence intensity; SD, standard deviation

Notes: Study 02 and Study 03 were conducted in Sweden, where desensitisation programs do not currently exist.
cPA: Anti-HLA analysed by central reading by Hansa Biopharma AB, Lund. SWE. Calculated using the cPRA calculator hosted by OPTN (UNetSM computer system) (cut-off >2,000 MFI)

Source: CS, Appendix C, Table 36, p.97 and clarification response A11

Appendix B: Clinical effectiveness outcomes in the decision problem cohort

Clinical efficacy evidence for the decision problem cohort, as reported by the company, is reported in Table 24 below. The company did not report any data in the CS for the following scoped outcomes: time to graft failure; time to rejection; time to next renal replacement therapy; time to rebound concentration of antibodies; hospitalisation days; and health-related quality of life (HRQoL).

Table 24: Clinical efficacy evidence for the decision problem cohort in the CS

Scoped outcome	Reported outcome	Subgroup analysis of the decision problem cohort Sample size: n = 25; final follow-up: 6 months
Efficacy on crossmatch conversion	Proportion of patients exhibiting a crossmatch conversion (all measures/timepoints) (CS Document B, p. 82-83)	N = 24/25 (96.0%)*
	Proportion of patients exhibiting mean MFI <3000 for all DSAs (SAB assay) (CS Document B, p.. 83)	2h post imlifidase [redacted] 24h post imlifidase: [redacted]**
	Change in total MFI load (SAB assay) (CS Document B, p. 83)	Baseline mean (SD): [redacted] Result mean (SD): [redacted]; median (IQR): [redacted]
Kidney function (eGFR)	Proportion of patients with eGFR at specific thresholds at final follow-up (CS Document B, p. 83)	>60mL/min/1.73m^3: 8/20 (40%) 30-59 mL/min/1.73m^2: 10/20 (50%): 1<30 mL/min/1.73m^2: 2/20 (10%) Missing: 5/20 (20%)
Time to graft failure	Proportion of patients with a functioning graft at final follow-up (CS Document B, p.84)	24/25 (96.0%)
Time, type, and incidence of rejection	Proportion of patients with biopsy-confirmed AMR	10/25 (40.0%)

Scoped outcome	Reported outcome	Subgroup analysis of the decision problem cohort Sample size: n = 25; final follow-up: 6 months
	(CS Document B, p.85)	
Time to rebound concentration of DSAs; proportion of patients who require treatment of rebound antibodies	MFI levels at various timepoints following transplant (CS Document B, p.83)	Mean (SD), median (IQR) Baseline: [redacted]; median [redacted] Day 7: [redacted]; median [redacted] Day 14: Mean [redacted]; median [redacted] Day 30: Mean [redacted] (MR); median [redacted]
Mortality	Overall survival at final follow-up (CS Document B, p.84)	25/25 (100%)

Abbreviations: AMR, antibody-mediated rejection; CS, company submission; DSA, donor-specific antibodies; MFI, mean fluorescence intensity; SAB, single antigen bead; SD, standard deviation

*The one remaining patient had borderline flow crossmatch and negative virtual crossmatch. This was not considered clinically significant and the transplant was carried out. **The Remaining four were confirmed to be due to single chain IgG which have highly attenuated activity compared to IgG. This is considered a false positive by the company.

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ERG report – factual accuracy check and confidential information check

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 20 November 2020** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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Issue 1 Definition of the imlifidase target population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 24, "*Imlifidase has a conditional marketing authorisation[12] to treat those unlikely to receive a transplant under the existing protocols of the KOS. This is defined by the company as those with a cRF over 95% with a positive crossmatch test to an available donor.*"	"*Imlifidase has a conditional marketing authorisation[12] to treat those unlikely to receive a transplant under the existing protocols of the KOS. This cannot be defined based on cRF alone, and this should be judged on a case-by-case basis by the treating physician.*"	The indication of imlifidase as included within the SmPC is as follows, "Idefirix [imlifidase] is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix [imlifidase] should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients." Hansa has never tried to define the imlifidase target population based solely on cRF/cPRA levels. The criteria stated by the ERG (≥95% cRF and positive crossmatch) were used to define a group for analysis from within the clinical trial populations that is as closely representative of the population covered by the marketing authorisation of imlifidase as possible. This group was labelled as 'unlikely to be transplanted', but this was intended only as a label for this group and not as a definition for what should be considered more widely as unlikely to be transplanted patients. Hansa does not believe that arbitrary cut-offs in cRF values can be used to accurately define imlifidase eligible patients. Hansa notes, in addition, that the 'unlikely to be transplanted' analysis group was derived from the available clinical	This is not a factual inaccuracy in that it reflects the evidence submitted by the company to substantiate effectiveness for this group of 'highly sensitised' patients. No change made.

		trial patients to be representative of the licensed population of imlifidase, and that this analysis group was derived to provide a dataset that could be used as a tool for discussion across different European countries with different KOS/priority access schemes. Within the CS (on pages 23/24), Hansa clearly states the criteria that should be used to define the population eligible for imlifidase. Hansa believes that the decision as to which patients remain unlikely to be transplanted should be determined by the treating physician as this is a complex determination that cannot be linked to cRF/cPRA values alone and is determined by the particular immunological profile of a patient. Hansa also notes that clinical advice to the ERG reported on page 24 of the ERG report states that the unlikely to be transplanted group is clinically recognisable. In addition, it is also noted that a positive crossmatch has no predictive value of likelihood of future transplant as a crossmatch is determined versus a specific donor. Therefore, this factor cannot be seen to be predictive of whether a patient is unlikely to receive a future transplant.	
On page 28, "*However, at clarification [A8], the company propose that a minority of patients that may receive imlifidase fall outside the*	*"At clarification [A8], the company made clear that a minority of patients that may receive imlifidase fall outside the definition of the 'unlikely to be transplanted'*	As outlined above, Hansa has never tried to define the imlifidase target population based solely on cRF/cPRA levels, and the 'unlikely to be transplanted' group was defined purely for analysis purposes. At clarification, it	This is not factual inaccuracy; the ERG statement is correct.

'unlikely to be transplanted' group. These patients were defined as patients with a sensitisation in the range 85–95% but have a particular immunological profile that makes them unlikely to receive a transplant (e.g. high total mean fluorescence intensity (MFI) load and/or a number of problematic DSAs."	*analysis group. These patients were defined as patients with a sensitisation in the range 85–95% but have a particular immunological profile that makes them unlikely to receive a transplant (e.g. high total mean fluorescence intensity (MFI) load and/or a number of problematic DSAs*."	appeared that the ERG was incorrectly interpreting the ≥95% cPRA/cRF threshold as the definition for imlifidase eligibility. Hansa's response at clarification attempted to make clear to the ERG that this threshold was used to define the 'unlikely to be transplanted' analysis group, and that there would be an expectation that a small minority of patients may fall below this threshold under particular circumstances. The wording within the ERG is not a factually correct representation of Hansa's position and communications.	
On page 67 the definition of the model population is unclearly and incorrectly defined, "*The model considered people with ESKD who are 'highly sensitised', which the company defined as ≥99% rather than the typical definition of ≥85% crossmatch positive*."	"*The model considered people with ESKD who are 'highly sensitised', and are unlikely to be transplanted under the KOS*."	The population considered by the economic model is wrongly stated to be ≥99% (no units, but assumed to mean cRF). The population considered by the model is clearly stated on page 100 of the CS, "*The patient population being assessed within this economic evaluation are those patients that fall within the licensed indication for imlifidase. This can be summarised as adults with chronic kidney disease awaiting a kidney transplant from a donor, who are highly sensitised with HLA, have a positive crossmatch with the donor, and are unlikely to be transplanted under the available KOS (after consideration of the revised version of the KOS).*" Therefore, the assertion that the definition of highly sensitised does not match the typical definition is not correct and should be deleted.	The ERG has amended this sentence to reflect the company's clinical evidence and to clarify that cRF is the key unit. Refer to ERG report Sn 4.2.3, p67

		Finally, it is stated that the typical definition of highly sensitised patients is ≥85% crossmatch positive. This is not a correct definition and should refer to ≥85% cPRA/cRF as the definition of highly sensitised, with no mention of crossmatch testing.	

Issue 2 Marketing authorisation of imlifidase

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 28 the marketing authorisation is incorrectly stated, "*The conditional marketing authorisation (CMA) for imlifidase states that patients have a cRF ≥95% and be considered 'unlikely to receive a transplant' through existing systems.*"	"*The conditional marketing authorisation (CMA) for imlifidase states that patients are highly sensitised and be considered 'unlikely to receive a transplant' through existing systems.*" This updated sentence accurately reflects the licensed indication for imlifidase.	The licensed indication for imlifidase, taken from the SmPC, is as follows: "*Idefirix [imlifidase] is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix [imlifidase] should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.*" The licensed indication only refers to patients being highly sensitised and does not define a cPRA/cRF value for this. Highly sensitised patients have an accepted definition of ≥85% cRF in the UK (as noted by the ERG on page 23 of their report).	The ERG has accepted this change and has edited the paragraph to specifically note the difference between the clinical evidence presented and the definition of highly sensitised used in the UK. Refer to ERG report Sn 2.4, p28
On page 28, "*The ERG considered this population to be outside of the current license for imlifidase, and was therefore beyond the scope of this appraisal.*"	Delete sentence as the group discussed (patients with a sensitisation in the range 85–95%) clearly falls within the licensed indication for imlifidase.		
On page 49, "…*the ERG noted that the range of cPRA starts at 88% (still within the definition of*	"…*the ERG noted that the range of cPRA starts at 88% (still within the definition of highly sensitised),*…."	As outlined above, the licence for imlifidase is mis-stated, as it covers highly sensitised patients, which is defined as a cPRA/cRF of	The ERG has clarified that this refers to the definition of 'unlikely to transplant' used by the company.

sensitised, but outside of the licence for imlifidase),…."		≥85%.	Refer to ERG report Sn 3.2.3, p49

Issue 3 Kidney allocation scheme

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 25, "… *the ERG considered it possible that if treatment with imlifidase increases the donor pool for those patients with cRF >95%, and these patients continue to be prioritised with the changes to the KOS algorithm introduced in 2019, then patients not within this group may be disadvantaged by comparison.*"	Addition of caveats to note that imlifidase is intended to be used for patients who remain disadvantaged despite the recent changes to the KOS, and that this would therefore not be expected to lead to a significant disadvantage to other groups above that already imposed by the KOS.	Within the CS (on pages 23/24), Hansa clearly states that to be considered for imlifidase, "*The patient remains unlikely to be transplanted, despite the revised KOS (Tier A or Tier B)*". Hansa intends that imlifidase would fit within the revised KOS and provide greater access to patients who remain unlikely to be transplanted even after consideration of the recent changes (and wording to this effect is included within the indication for imlifidase). Hansa also believes that the primary benefit in the revised KOS is for the patients with the highest levels of sensitisation (Tier A consists of patients with a matchability score of 10/cRF 100%). There therefore remain patients who are not significantly advantaged by the updated KOS, and these patients are those for whom imlifidase would provide a benefit. Hansa also believes that disadvantage for patients outside this group is not correctly considered by the ERG. In providing preferential access to more highly sensitised patients, the KOS balances a	This is not a factual inaccuracy. The ERG considered the potential impact of a change in the allocation of the donor pool on the KOS to be a valid consideration.
On page 25, "*It is not known whether it would be appropriate to adjust the KOS algorithm to ensure equality of access if imlifidase were to be introduced. The company provided no comment on this*…"	Remove the comment that the company provided no comment on this, in a number of places within the CS (page 21, for example) Hansa states that imlifidase should be targeted at those patients who remain unlikely to be transplanted despite the KOS. Hansa intends that imlifidase should be used within the structure of the KOS as it is now structured, as this treatment will increase equity of access to a small patient group that is currently significantly		This is not a factual inaccuracy. The ERG statement is regarding whether a change in the KOS algorithm would be necessary to ensure equality of access across the broader pool of patients on the waiting list for kidney allocation.

	disadvantaged.	trade-off between giving each kidney to the optimal recipient and an equitable distribution of kidneys. This trade-off is justified by the fact that the disadvantage for highly sensitised patients outweighs the minor disadvantages to less sensitised patients, as these patients are far more likely to achieve another match. The addition of imlifidase to this should not fundamentally alter this balance, as imlifidase should remain targeted to patients who remain unlikely to receive a transplant despite the KOS (and wording to this effect is part of the marketing authorisation for imlifidase). Hansa also notes that consideration of the wider kidney transplant population falls outside the defined population of this appraisal, as included within the scope.	
On page 69, "*Furthermore, in having spent less time on dialysis, and not having antigens, it is possible (and potentially likely at the aggregate level) that the alternative recipient may achieve a better outcome from transplantation than the imlifidase patient.*"	Delete sentence; this falls outside the scope of the appraisal, or include the addition of caveats that any disadvantage would be minor compared to the current disadvantage experienced by patients unable to receive a timely transplant due to high sensitisation.		This is not a factual inaccuracy. The ERG statement is within a discussion about the remit of the scope for this appraisal. The ERG believe that this is an issue for consideration.

Issue 4 ERG data obtained from NHSBT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34, "*Data received by the ERG from NHSBT shows that a significant minority of patients do not receive dialysis.*"	Add a caveat around the population analysed within these data and the differences to the imlifidase eligible population.	The data obtained by the ERG from NHSBT is described as being for a group of patients with cRF ≥99%. This group does not match the proposed eligible population for imlifidase. In particular, as highlighted a number of times, cRF values alone cannot be used to define an eligible population for imlifidase as this cannot identify patients who are unlikely to be transplanted. There	This is not a factual inaccuracy. The ERG has sought the best available data on UK practice. The ERG noted the comment by the company about the importance of cRF values; however, the ERG also noted that there is no established criteria for defining those patients who are unlikely to receive a transplant under

		have been developments in clinical practice that have led to the early (pre-emptive) listing of patients who will require a kidney transplant, at a point before they require dialysis. This practice has become particularly common for highly sensitised patients (to maximise their ability to receive a timely transplant), but at the point of being listed most of these patients cannot be considered unlikely to be transplanted. As the data obtained by the ERG shows, a significant minority of these patients will receive a transplant. Advice received by Hansa indicates that the majority of these transplants occur within the first 18 months of listing and are not down to luck, but are due to the immunological profile of these patients. This patient population with a high cRF is therefore not representative of an unlikely to be transplanted patient group, and this is clearly illustrated by the proportion of these patients who were not on dialysis. In contrast, all deceased donor transplanted patients within the imlifidase clinical trials had been receiving dialysis before their transplant, in many cases for considerable numbers of years. As the patient group utilised by the ERG cannot be considered to consist of unlikely to be transplanted patients, they would not fall under the licensed indication for imlifidase and hence cannot be considered as a relevant group for this appraisal. Hansa also finds it very unclear why a cRF	the current KOS. In the absence of such criteria, the ERG believed that the use of a 99% cRF threshold is a reasonable proxy to provide information about the target population. To this end a new section has been added (Section 6.1) discussing this approach explicitly. Refer to ERG report: Sn 6.1, p86
On page 67, "*It is possible that the more highly sensitised patients (cRF ≥99%) may be more likely to require a second dose and as a result*…"	Remove this sentence as the group being quoted does not reflect the group of imlifidase eligible patients.		This is not a factual inaccuracy as patients with cRF ≥99% may fit within the target population, and therefore this statement is relevant to the pattern of treatment required in the target population. However, in acknowledgment that a threshold of 99% cRF is not an absolute definition of highly sensitised, we have removed the 99% cRF criteria from this statement (p.68). Refer to ERG report: Sn 4.2.4.1, p68
On page 69, "*The ERG requested and received data from NHSBT[9] on the treatments received by highly sensitised patients on the transplant waiting list. The data from NHSBT provided to the ERG is presented in Table 13*…"	Add a note around the population included and the differences to the imlifidase eligible population.		This is not a factual inaccuracy; however, the ERG has added Section 6.1 to discuss explicitly the approach taken to operationalising the company's patient group definition. Refer to ERG report: Sn 6.1, p86
On page 77, "*This presented a difference from the CS, but is*	Add a note around the population included and the differences to the		This is not a factual inaccuracy; however, the ERG has added Section

taken from the latest data on the highly sensitised (≥99%) group…"	imlifidase eligible population.	value of ≥99% has been chosen by the ERG, as this does not match any values included within the CS.	6.1 to discuss explicitly the approach taken to operationalising the company's patient group definition. Refer to ERG report: Sn 6.1, p86
On page 89, "*However, data provided by NHSBT[9] in the highly sensitised group (≥99%)*…"	Add a caveat around the population analysed within these data and the differences to the imlifidase eligible population.		This is not a factual inaccuracy; however, the ERG has added Section 6.1 to discuss explicitly the approach taken to operationalising the company's patient group definition. Refer to ERG report: Sn 6.1, p86
On page 93, "…*to a patient not requiring imlifidase (who may or may not be in the >99% sensitised group)*."	Remove the reference to >99% sensitisation as this is not relevant to imlifidase eligible population.		This is not a factual inaccuracy; however, the ERG has added Section 6.1 to discuss explicitly the approach taken to operationalising the company's patient group definition. Refer to ERG report: Sn 6.1, p86
On page 19, "*Following a request from the ERG, data was provided by NHS Blood and Transplant for this patient group which informs the model and reduces the uncertainty around this aspect*."	"*Following a request from the ERG, data was provided by NHS Blood and Transplant on a group of very highly sensitised patients which reduces the uncertainty around this aspect*."		The company's proposed wording has been accepted; this reflects that there is likely a large degree of overlap between the populations, albeit not a perfect one. Refer to ERG report: Sn 1.5, p19

Issue 5 Study 02

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 42, the description	"*Patients in Study 02 did not*	As stated, transplant was not a defined part	This is not a factual inaccuracy.

around the transplanted patient in Study 02 is not correctly presented, "*Patients in Study 02 did not receive a transplant as part of the trial protocol, and therefore the single participant (1/8, 12.5%) who received a transplant during follow up did so incidentally*."	*receive a transplant as part of the trial protocol, and therefore a single participant (1/8, 12.5%) received a transplant as this possibility arose for them*."	of the protocol for Study 02, but this was performed at the discretion of the investigator if the possibility arose. Therefore, kidney transplant was not the objective of the study but was accommodated for should favourable conditions arise. As such, was by no means 'incidental'.	Transplant was not specified within the trial protocol, therefore the ERG statement is correct.

Issue 6 ITT population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 50, "*The ERG was also concerned that discrete event data following transplant were generally presented in samples only including patients who exhibited a crossmatch conversion and transplant following treatment with imlifidase, rather than the ITT population.*"	Delete this statement.	All patients who received a full dose of imlifidase achieved crossmatch conversion (except for the single patient who had a negative virtual crossmatch and positive flow crossmatch, which was judged as not clinically significant and transplant was carried out). Only a single patient in line for transplantation (in Study 06) had their infusion interrupted and therefore did not receive a transplant. The statement from the ERG is therefore illogical and incorrect. Discrete transplant event data were reported for all patients that received transplant. This has to be considered as the ITT population in this case, as these data do not exist for patients that were not intended to be transplanted and did not receive a transplant.	This is not a factual inaccuracy and in fact reflects tautological reasoning on the part of the company. Specifically, the company seem to be suggesting that receipt of imlifidase for an ITT population is precisely coterminous with those who received a transplant, or possibly a transplant from a deceased donor. This is, unto itself, a logical fallacy in that it begs the question of the effectiveness of imlifidase. The company's approach to outcome assessment generally considered only those patients who received a full dose of imlifidase, exhibited a crossmatch conversion, and received a transplant. A perspective considering all patients who entered

			the included trials (ITT) would have been a more robust approach to evaluating the effectiveness of imlifidase.

Issue 7 Crossmatch conversion and transplantation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG has conflated crossmatch conversion (to negative crossmatch) and the ability to receive transplant within the first paragraph of page 68. In particular, "*The patient who did not achieve a negative cross match went on to receive a transplant regardless as they were assumed to be appropriate for the transplant however, the company's modelling approach does not capture the fact that a negative crossmatch was not obtained through imlifidase use*."	"*The patient who did not achieve a negative cross match (flow crossmatch, but did achieve negative virtual crossmatch) went on to receive a transplant regardless as they were assumed to be appropriate for the transplant.*"	Crossmatch conversion was the key endpoint for the clinical trial data, as a negative crossmatch is indicative that the transplant can successfully proceed. However, as highlighted by the case of this individual patient, the failure to achieve a negative crossmatch does not necessarily preclude a successful transplant occurring (however, clinical judgement would be required in these cases). When considering the economic modelling of imlifidase, whether or not transplant successfully occurs is the key point, and the fact that a negative crossmatch was not obtained is not relevant when in the one case where this occurred during the imlifidase clinical trial programme there had been clear efficacy of imlifidase and a borderline positive flow crossmatch result was obtained which allowed the transplant to proceed successfully. Hence, Hansa believes that it is fair to consider that this individual case, where transplant was able to successfully proceed, should not be	This is not a factual inaccuracy; The ERG believed this remains an issue that not all patients will achieve a negative crossmatch even if it may be *assumed* that a patient is able to receive a transplant. The ERG believed that the individuals' observed data should be included in the model and not censored, though whether this should be classed as a success (a transplant occurred) or a failure (the transplant occurred despite crossmatch not being a success) is, in the ERG's opinion, a legitimate question. To this end, further discussion has been added, and calculations changed in the ERG base case classing this patient as a success (though varying this in sensitivity analysis). These changes can be seen on Page 68. Refer to ERG report: Sn 4.2.4.1, p68

Also on page 68, "*The proportion of patients to undergo transplant following imlifidase is calculated by multiplying the proportion of patients to receive a full dose of imlifidase (53 out of 55 by the proportion of patients that achieved a negative cross match (52 out of 53 who received the full dose).*"	"*The proportion of patients to undergo transplant following imlifidase is calculated by multiplying the proportion of patients to receive a full dose of imlifidase (52 out of 54 by the proportion of patients that achieved a complete negative cross match (45 out of 46 who received the full dose).*"	included within the model. In addition, the numbers included by the ERG in regard to these issues are not correct, 54 patients received dosing with imlifidase and 2 of these patients received incomplete dosing (see Table 22 of CS, p87). A single patient (who did receive a full dose of imlifidase) did not achieve a negative crossmatch before transplant (this was a negative flow crossmatch, and a negative virtual crossmatch was achieved for this patient who successfully received a transplant as the result was considered clinically not significant); however, as crossmatch is only evaluated in relation to the specific donor it would be more correct to state that 45 out of 46 of transplants (who all received a full dose of imlifidase) achieved a complete negative crossmatch. The additional Phase II trial 13-HMedIdeS-02 (n=8) was performed in sensitized 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, PK/PD, safety study.	Changes made. Refer to ERG report: Sn 4.2.4.1, p68
Also on page 68, 94.5% is stated to be the proportion of patients receiving transplant following imlifidase infusion.	This should be corrected to 96.3% (52/54) as the patient who did not achieve a complete negative crossmatch was able to successfully receive a transplant.		Changes made. Refer to ERG report: Sn 4.2.4.1, p68
On page 87, "*Although the rate is clearly high, one patient failed to achieve a negative crossmatch (and received a transplant regardless)*"	"*Although the rate is clearly high, one patient failed to achieve a negative FACS crossmatch (and received a transplant regardless as a negative virtual crossmatch result was achieved and the transplant proceeded based on clinical judgement)*"		Changes made to reflect patient achieving a negative virtual crossmatch (p. 87). Refer to ERG report: Sn 6.3.1, p88
On page 88, "*As the true rate of crossmatch conversion is unknown the ERG has adjusted the proportion to receive transplant in the intervention arm by accounting for the patients who did not receive the full dose and the patient who did*	"*As the true rate of transplantation following imlifidase is unknown the ERG has adjusted the proportion to receive transplant in the intervention arm by accounting for the patients who did not receive the full dose and the patients who did not successfully receive a*		The company's proposed proportion of patients to receive a transplant in the imlifidase arm accepted. ERG original assumption to account for failure to convert to negative FACS crossmatch explored as an additional scenario analysis (p. 88).

not achieve a negative crossmatch. This resulted in a rate of transplant for the imlifidase arm of 94.5% as opposed to the 100% in the company submission."	*transplant. This resulted in a rate of transplant for the imlifidase arm of 96.3% as opposed to the 100% in the company submission.*" [This correction will impact the ICER reported]		Refer to ERG report: Sn 6.3.1, p88
In a number of places where the ERG additional analyses are reported, the erroneous figure of 94.5% has been used. These are: Table 2, p20; Table 19, p.95; page 96, point 1; Table 20, p97, page 101.	This should be corrected to 96.3% (52/54) as the patient who did not achieve a complete negative crossmatch was able to successfully receive a transplant. The associated ICERs for these analyses will also then need to be recalculated using this corrected value.		The company's proposed proportion of patients to receive a transplant in the imlifidase arm accepted. ERG original assumption to account for failure to convert to negative FACS crossmatch explored as an additional scenario analysis. Refer to ERG report: Sn 1.7 (Table 2) (p21); Sn 4.2.4.1, p68; Sn 6.3.1, p88; Sn 6.3.13 (Table 19) (p96); Page 97; Sn 6.4.1 (Table 20) (p98-99); Sn 6.4.1 Table 21 (p99); Sn 6.4.1.1 (Table 22) (p100), Sn 6.4.1.1 (Figure 5) (p103); Sn 6.4.1.1 p104.
On page 67, "*There are likely to be some patients (three out of 55 in the clinical trial program, based on the company's clarification response A13) who receive imlifidase but, due to infusion related reactions or failure to achieve a negative crossmatch, are not able to go on to transplant*."	"*There are likely to be some patients (two out of 54 in the clinical trial program, based on the company's clarification response A13) who receive imlifidase but, due to infusion related reactions or failure to achieve a negative crossmatch, were not able to go on to transplant*." The values of 3 out of 55 were not provided within clarification response A13, and the correct		Changes made. Refer to ERG report: Sn 4.2.3, p67

	values should be used as reported in that response.		
On page 51, "…*the ERG was aware that the FACS and CDC crossmatch tests are most commonly used in the UK, but only 23/46 (50.0%) of transplanted patients in the included trials were evaluated for a crossmatch conversion using the FACS*…"	"…*the ERG was aware that the FACS and CDC crossmatch tests are most commonly used in the UK, but only 31/46 (67.4%) of transplanted patients in the included trials were evaluated for a crossmatch conversion using the FACS*…"	The number of patients assessed by FACS crossmatch tests is incorrectly stated by the ERG.	The ERG welcomed this clarification from the company on the number of FACS tests conducted to evaluate crossmatch conversion. The ERG has corrected these figures in the ERG report (p51), however, a note has also been added that this figure could not be validated by the ERG, and was inconsistent with information provided in the CS, Refer to ERG report: Sn 3.2.4.1, p51
On page 51, "… *and only 2/46 (4.3%) of transplanted patients were evaluated using CDC.*"	"… *and only 21/46 (45.6%) of transplanted patients were evaluated using CDC.*"	The number of patients assessed by CDC crossmatch tests is incorrectly stated by the ERG. The CDC crossmatch test was not performed at all trial sites, but 21 pre-dose tests were performed and 9 post-dose tests were performed (a post-dose test was not performed when not necessary, for example the pre-dose CDC test was negative).	This is not a factual inaccuracy. The statement refers to testing for crossmatch conversion in patients who received a transplant. In their response the company propose include pre-dose testing rates and rates of conversion in patients who did not receive a transplant (those with a hypothetical donor). The company's proposed revision is therefore factually incorrect.

Issue 8 Comparator in cost-economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG has misstated the reality for patients who do not receive imlifidase. On page 18, "*In reality not all patients who receive imlifidase are able to receive a transplant, and not all patients who are untreated with imlifidase are necessarily on dialysis or fail to receive a transplant – particularly in light of the revised KOS, where greater priority is given to highly sensitised patients*."	"*In reality not all patients who receive imlifidase are able to receive a transplant, and patients who are untreated with imlifidase are highly unlikely to be transplanted*."	The licensed indication for imlifidase includes the restriction that treatment "…*should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients*." The assertion by the ERG that "*not all patients who are untreated with imlifidase are necessarily on dialysis or fail to receive a transplant*" is therefore in conflict with the indication. For a patient to be eligible for imlifidase treatment they have to be unlikely to be transplanted (with consideration of the KOS). There remains a very low chance that these patients would receive a transplant without imlifidase. The ERG also mentioned that not all patients who do not receive imlifidase would be receiving dialysis. However, Hansa finds this to be factually inaccurate. There is often pre-emptive listing of patients who will require a kidney transplant before they require dialysis. This practice has become particularly common for highly sensitised patients, but at the point of being listed most of these patients cannot be considered unlikely to be transplanted, as a significant minority of these patients will receive a transplant within the first 18 months of listing. This ability to receive a transplant is	This is not a factual inaccuracy, and indeed is a restatement of the same issue; that patients in the comparator arm are 'highly unlikely' to receive a transplant in the words of the company, but 'not all will fail to receive a transplant' in the words of the ERG i.e. the rate is non-zero. The data obtained by the ERG from NHSBT showed that not all patients on the transplant waiting list in the cRF ≥99% group were receiving dialysis treatment. The ERG is using these data to inform the model as the group provide a reasonable proxy for the population of interest in the absence of an explicit definition for the patients considered eligible for imlifidase (as this patient group is difficult to define).
Page 69, "*The ERG notes that the comparator in the model should allow a proportion of patients to receive no dialysis to align with current practice*…"	Delete this erroneous statement		This is not a factual inaccuracy; data from NHSBT in a highly sensitised population, and validated by clinical input show this to be the case. The company's inputs for dialysis are taken from a wider transplant population, and a transplant rate set to zero is in conflict with their justification that: "There remains a very low
Page 89, "Allowing 31.44% of dialysis patients to receive a transplant resulted in an ICER change from £31,971 to	Delete this analysis based on incorrect assumptions		

£59,335."		not simply down to luck, but is due to the particular immunological profile of these patients. Therefore, it is clear that imlifidase patients, by virtue of being unlikely to be transplanted, will be receiving dialysis. This fact is illustrated as all deceased donor transplanted patients within the imlifidase clinical trials had been receiving dialysis before their transplant, in many cases for a considerable number of years. In addition, the ERG has made a logical error in their decision making that renders the decision factually incorrect. The ERG state that the appropriate comparator should match the NICE scope and therefore include "*Adults with chronic kidney disease awaiting a kidney transplant from a donor, who are highly sensitised with human leucocyte antigens (HLA) and have a positive crossmatch with the donor*" (copied from the scope). This is used to justify the fact that patients in the comparator arm should be able to receive transplant. However, as outlined within the CS and elsewhere, imlifidase is not an appropriate or licensed treatment across this whole population and it's licensed for use only in patients who are unlikely to receive a transplant. Therefore, under the logic applied by the ERG, the imlifidase arm of the model should only have included a small proportion of patients receiving imlifidase (to reflect the limited eligibility within this wider population). This logic has not been applied by the ERG, and only	chance that these patients would receive a transplant without imlifidase." The company also noted the history of the clinical trial patients, who were not necessarily reflective of the patients for whom approval is being sought, as has been seen with other treatment practices such as the type of crossmatch testing used. In terms of the NICE scope, the ERG believed that the use of the highly sensitised population eligible for imlifidase to be appropriate, and has endeavoured to populate the model with inputs appropriate to this group where none were provided by the company. As such the comments on the scope do not represent a factual inaccuracy, but a (legitimate) disagreement regarding inputs, for instance on the rate of transplantation in each arm; as the company acknowledge the rate is non-zero (which was the rate used in their submission), with the ERG taking data from NHSBT on observed outcomes for this patient group.
The ERG analysis of "Allow a proportion of dialysis patients to receive a transplant" in the following locations: Table 2, page 20; Table 19, page 95; Table 20, page 97	Delete this analysis based on incorrect assumptions		

		changes to the comparator arm have been made. Hansa considers such modelling would seem to be of little value where the majority of patients would be receiving identical treatments on both sides of the comparison (e.g. no dialysis and transplant without imlifidase). Therefore, the economic model focussed on the group of patients who are eligible for imlifidase. Hansa considers that this error within the ERG's considerations so great that this is a clear factual error, rather than simply a difference of opinion over the most appropriate assumptions to be used within the economic modelling.	

Issue 9 Li *et al*. utility study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 73, "*On careful reading of the Li et al.[43] study, of the 1,070 patients classified as on the waiting list for transplant, only 98 were pre-dialysis (the reason given by the company for not using the data was that it includes non-dialysis patients)*."	"*On careful reading of the Li et al.[43] study, of the 1,070 patients classified as on the waiting list for transplant, only 98 were pre-dialysis (one of the reasons given by the company for not using the data was that it includes non-dialysis patients)*."	Hansa did not state that Li *et al*. was not used within the base case analysis only because it included non-dialysis patients. A full critique and reasoning was presented on page 121 of the company submission, where the inclusion of non-dialysis patients was outlined a key issue. However, Hansa had a number of further concerns with this study including: quality of life (QoL) measures were not a primary outcome; study design did not prioritise these QoL data (for example, a low completion rate was evident in the QoL data, leading to the potential of bias from this missing data);	Text changed on page 73 to reflect this being the main reason Refer to ERG report: Sn 4.2.7, p74

		matching within the study between waiting list patients and transplant recipients was done for the purpose of studying survival and not for the measurement of health status (hence important factors in relation to QoL were not matched); the QoL questionnaire was administered by nursing staff in the hospital/caring environment; data were reported using EQ-5D-5L without sufficient detail to allow transformation to EQ-5D-3L. Given all of these facts, Hansa strongly felt that the Liem *et al*. publication provided more robust data in a measure preferred by NICE (EQ-5D-3L), despite the age of this study.	
On page 19, "*The ERG performed a literature search, which identified a systematic review of utility values published after the CS (Li et al., 2017).*"	Correct this sentence, probably to refer to Cooper *et al*. rather than Li *et al*.	The Li *et al*. study was identified by Hansa and was included within the CS. This study was also not a systematic review of utilities, and hence this sentence is not factually correct and is unclear as to its intended sense. Hansa assumes that this should refer to the Cooper *et al*. publication.	Correction made – the company are correct this is a reference error. Refer to ERG report: Sn 1.5, Key Issue 7, p19

Issue 10 Time of action for imlifidase

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Key Issue 2 on page 14, it is stated that, "There is a further lack of clarity around the time required for imlifidase to act…"	Correct this statement to match the data included in SmPC (and which was supplied to NICE as part of the submission documentation).	The SmPC includes the following, "*PKPD modelling showed that at 2 hours after administration of 0.25 mg/kg imlifidase, a crossmatch test is likely to become negative in 96% of the patients, and after 6 hours at least 99.5% of the patients are*	This is not a factual inaccuracy. The ERG noted that at clarification (A18) the company stated that imlifidase requires between 2 and 6 hours to act before transplant can occur. However, a 4-hour window conveys significant

		likely to become crossmatch test negative."	uncertainty when reducing the cold ischaemic time of the donor kidney is paramount for patient outcomes. The ERG considered there to be outstanding uncertainty for clinical practice in when to perform a crossmatch test, and to what extent the wait for imlifidase to act will impact on clinical practice.
On page 25, "*Further guidance from the company is needed to determine at what time point following imlifidase infusion a crossmatch test should be carried out in practice to identify a crossmatch*…"			This is not a factual inaccuracy; please see comment above.
On page 25, "*In one of the included trials, the reduction in median DSA levels reached their lowest between a range of* [redacted] *after treatment*…"	Add a caveat that the absolute lowest DSA value does not determine the time point at which transplant can occur.	The time at which the lowest DSA values occur does not provide a representation of when conversion to negative crossmatch may have occurred. The SmPC statement included above shows the time points at which a negative crossmatch is expected to occur.	This is not a factual inaccuracy. This statement by the ERG conveys the variation in the response of DSA levels between patients treated with imlifidase, and supports comments above about the need for further guidance from the company on the placement of imlifidase in the treatment pathway.

Issue 11 Adverse event reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 57, "…*in the decision*	"…*in the decision problem cohort*	The data referred to by the ERG was for	This is not a factual inaccuracy: the

problem cohort exhibited a severe adverse event, labelled as 'non-SAE'…"	*exhibited a treatment-related severe adverse event, labelled as 'non-SAE'…*"	treatment-related severe non-serious AE (SAE), and so this should be accurately reported as such.	event is a severe 'non-SAE' event. The ERG noted in Table 8 of the ERG report (p.58), that the company determined this event to be treatment-related.
On page 57, "*The most common SAEs were transplant rejection …; Section 3.2.4.4) infections (Section 3.2.4.7)*"	"*The most common SAEs were transplant rejection …; Section 3.2.4.4) urinary tract infections (Section 3.2.4.7)*"	The SAE data referred to is urinary tract infections rather than just infections.	This is not a factual inaccuracy: urinary tract infections are infections.

Issue 12 Potential typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
One of the bullet points on page 12 states, "*Changing the comparator to standard case…*"	Hansa believes that this should have referred to standard care	The bullet as written does not make sense, Hansa believes that this is a simple typographical error that needs correcting to allow the true sense of the point to be clear	Change made Refer to ERG report: Sn, 1.1, p12
Within the descriptions of the countries where the trials were conducted on page 38, "…*and the USA (Study 04)*."	"…*and the USA (Study 04 and Study 06)*."	It appears that Study 06 has been erroneously missed from the studies conducted within the USA. This fact is correctly included in Table 5 which implies that this is a simple typographical error.	Change made Refer to ERG report: Sn, 1.1, p38
On page 41, "…*as compared to patients in Studies 02 and 04*.	Hansa believes that this should have referred to Studies 02 and 03.	Study 04 is referred to within both sides of the comparison made within this sentence. Hansa believes that this is a typographical error that should be corrected for clarity and accuracy.	Change made Refer to ERG report: Sn, 3.2.1.2, p.41
On page 42, "*Across the*	"*Across the included studies, a*	The text incorrectly refers to the trials where	Change made

included studies, a minority of patients who received a transplant received kidney from a living donor, which is not consistent with the CMA for imlifidase (Study 02: 1/1 [100%] patients transplanted; Study 06 5/18 [27.8%] patients transplanted)."	*minority of patients who received a transplant received kidney from a living donor, which is not consistent with the CMA for imlifidase (Study 03: 2/10 [20%] patients transplanted; Study 06 5/18 [27.8%] patients transplanted).*"	a living donor was used for the transplant, with the transplant in Study 02 coming from a deceased donor. These details are reported correctly within Table 6 of the ERG report and the text should be updated to match this.	Refer to ERG report: Sn, 3.2.1.2, p.42
On page 51, "*Finally, not all MFI levels were reported for patients with a matched donor and in reference to a DSA*…"	Remove the word matched, or add additional clarification.	Hansa assumes that this is an erroneous use of the word matched, as if a matched donor were present, this would be a compatible transplant for which imlifidase would not be necessary. It is assumed that this is not what was meant by the ERG in this case.	Change made Refer to ERG report: Sn 3.2.4.1, p51
Table 13 heading, page 69 "*cFR ≥99%*"	"*cRF ≥99%*"	A typographical error in cRF should be corrected.	Change made Refer to ERG report: Sn 4.2.4.2 (Table 13), p69
On page 74, "*Section 6.2.4 details the additional work performed by the ERG in implementing the utilities from Table 5 of Li et al.,*…"	Delete the reference to Li *et al*., or add this information to Section 6.2.4.	Section 6.2.4 does not contain any information on Li *et al*. and so this comment or Section 6.2.4 needs to be updated to correct for this.	Change made Refer to ERG report: Sn 4.2.7, p74
Page 107, reference 33 is missing	Add reference 33	An error appears to have occurred with the referencing such that reference 33 is blank, this should be corrected for transparency.	Change made Refer to ERG report: References, p108
Table 2, page 20	Add a row for "*Utility source – Cooper et al. (2020)*"	A row for "*Utility source – Cooper et al. (2020)*" is not included, despite this being	Change made

		one of the ERG preferred assumptions (as outlined in Table 20, p97 of ERG report). This should be included for completeness in Table 2.	Change made Refer to ERG report: Sn 1.7, p21
Table 23 page 110, the mean for Total time on dialysis in the 'All' group is incorrectly stated as [redacted], which is the value for the 'unlikely to be transplanted' analysis group.	Correct these data to [redacted]	The data from response A11 to the clarification questions have been incorrectly reproduced.	Change made Refer to ERG report: Appendix A, p111
Table 24, page 112. The * referenced in the footnotes has been omitted from the table.	Add the * which should be positioned after the data of proportion of patients exhibiting a crossmatch conversion, i.e. N = 24/25 (96.0%)*	This missing footnote link leaves important information not referenced to from within the table.	Change made Refer to ERG report: Appendix B, p113

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**ERG response**
ERG report, page 28 paragraph two	The marked sentence can be unmarked, as this information is included unmarked within the clarification questions responses.	These patients were defined as patients with a sensitisation in the range 85–95% but have a particular immunological profile that makes them unlikely to receive a transplant (e.g. high total mean fluorescence intensity (MFI) load and/or a number of problematic DSAs).	Change made Refer to ERG report: Sn 2.4, p28
ERG report, page 67 paragraph one	The markings within the proportions of patient receiving full dosing and negative crossmatch are	The proportion of patients to undergo transplant following imlifidase is calculated by multiplying the proportion of patients to	Change made Refer to ERG report: Sn 2.4, p68/69

ERG report, page 68 paragraph one	unnecessary as this information is included unmarked within the CS.	receive a full dose of imlifidase (52 out of 54 by the proportion of patients that achieved a negative cross match (45 out of 46 who received the full dose). The patient who did not achieve a negative cross match went on to receive a transplant regardless as they were assumed to be appropriate for the transplant however, the company's modelling approach does not capture the fact that a negative crossmatch was not obtained through imlifidase use. This resulted in an estimated 94.2% of patients to be transplanted following imlifidase infusion (52/54* 45/46) which was incorporated into the ERG base case with alternative proportions assessed in the sensitivity analysis to explore the impact of this assumption.	Change made Refer to ERG report: Sn 2.4, p68/69 Relatedly, we have unmarked the same data on p 88
ERG report, page 112 Table 24	The proportion of patients exhibiting a crossmatch conversion is unnecessarily marked as confidential as this data is included unmarked in CS.	24/25 (96.0%)	Change made Refer to ERG report: Appendix B, p113
ERG report, page 112 Table 24	Some MFI values are not correctly marked and should have AIC marking added	Change in total MFI load (SAB assay): Result mean (SD): [redacted]; median (IQR): [redacted] Mean (SD), median (IQR) Baseline: [redacted]; median [redacted] Day 7: [redacted]; median [redacted]	Change made Refer to ERG report: Appendix B, p113

		Day 14: Mean [redacted]; median [redacted] Day 30: Mean [redacted]; median [redacted]	
ERG report, page 112 Table 24 footnote	The footnote can be unmarked, as this information is included unmarked in CS.	*The one remaining patient had borderline flow crossmatch and negative virtual crossmatch. This was not considered clinically significant and the transplant was carried out.	Change made Refer to ERG report: Appendix B, p114

NICE National Institute for Health and Care Excellence

Technical engagement response form

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Monday 11 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Marcus Dahlman**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Hansa Biopharma AB**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Relevance of comparators and methodological uncertainty	**No**	Hansa is strongly of the opinion that the relevant comparator for this appraisal is as defined by the scope of this appraisal and as constrained by the licence of imlifidase. Hansa believes that the comparator as defined by the ERG is not correct. The relevant comparator for this appraisal is clinical management without imlifidase for the group of patients who would be eligible for treatment with imlifidase. This covers the small group of patients who remain unlikely to be transplanted even with consideration of the recently revised Kidney Offering Scheme (KOS). As outlined in the following sections, Hansa believes that the relevant comparator is therefore dialysis. Hansa believes from the available published guidance on NICE's processes and methods that the NICE terms of reference for an appraisal are constrained by the scope of the appraisal and the licence of treatments. As such, Hansa believes that the wider cost-benefit analysis proposed by the ERG falls outside the scope of this appraisal. One of the major advantages given by the introduction of imlifidase is greater equality of access to the current accepted standard treatment option for end stage renal disease, kidney transplant (this can also be phrased as equity in provision of transplant). Within the highly sensitised patient population there is a subgroup of patients that remain significantly disadvantaged by their inability to receive a transplant (the licensed and target patient population for imlifidase). These patients at best experience significantly increased wait times for transplant, and very many of these patients may never receive a suitable donor organ offer. This leads to

		significantly longer periods on dialysis (or an indefinite time on dialysis), and this is associated with declining health and quality of life. Many of these patients may become too sick to receive a transplant before one becomes available to them, and so lose the ability to ever access this accepted standard treatment. Others (due to their immunological profile) may never receive a suitable kidney offer. The significant unmet medical need in this small group of highly sensitised patients has been recognised by EMA, with imlifidase being developed with the support of the EMA PRIME scheme (which is available to medicines that target a particular unmet need), and through the orphan indication granted by EMA for imlifidase. Imlifidase provides an ability to enable a more equal access to kidney transplant for a currently disadvantaged group of patients who are unlikely to receive a transplant through other means. A purely utilitarian cost-effectiveness analysis on a whole population level (as proposed by the ERG as one of their additional scenario analyses) would fail to capture this primary benefit. This approach would also fail to account for the fact that kidney allocation of deceased donor kidneys through the KOS already relies on a degree of trade-off between equality of access to all patients and providing the best 'quality' in matching (NHS Blood and Transplant. Kidney Transplantation: Deceased Donor Organ Allocation. 2019). The recent changes made to the KOS are widely accepted to have been implemented with an aim of improving equality of access (that had not been addressed in other ways) by improving access to transplant for the more highly sensitised patients. Despite these changes having shown improvement in this regard, there are disadvantaged patients who do not benefit from the aims of this scheme and who remain unlikely to receive a transplant under the revised KOS. Imlifidase is a therapy option that enables access to transplant for these patients. This principle is included within the Conditional Marketing Authorisation for imlifidase which states that "*Idefirix [imlifidase] is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix [imlifidase] should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.*" The second half of the indication makes clear that imlifidase should be used for patients who remain unlikely to be transplanted despite consideration of available allocation schemes (living donor schemes and the KOS), and that these schemes should be

		utilised first before imlifidase is considered. Imlifidase can therefore be seen as a last line tool to assist implementation of the principles intended within the KOS of providing a more equal access for highly sensitised patients, with the intent that this treatment is used in the small patient group that remains disadvantaged and unlikely to receive a transplant otherwise. As outlined within the Company Submission, Hansa expects that the patient population eligible for imlifidase in the UK is a total of approximately 110 patients, with only a small proportion of these patients expected to receive a transplant each year with imlifidase (maximum of around 25-35 per year within the budget impact submission). In addition, Hansa believes that there are significant shortcomings in the ERG's consideration of this issue. Firstly, the comparator outlined by the ERG during economic modelling is inappropriate since it includes patients that do not match the indication of imlifidase, and hence the scope. The ERG has defined a group of highly sensitised patients as a supposed proxy for unlikely to be transplanted patients. However, the judgement of a patient to be unlikely to be transplanted is complex and includes more than just a cRF estimation, e.g. type and combination of HLA antibodies and time on dialysis. The data from NHSBT show a high rate of transplant in the suggested comparator group, and hence there are many of these patients who would not be considered to be unlikely to be transplanted. The feasibility of transplants for many of the patients within this group are not down to chance alone and are able to occur as a suitable living donor is available, or as that patient's particular immunological profile is not overly problematic or uncommon. However, beyond these patients with a reasonable chance of transplant is a group that are unlikely to receive a transplant and fall within the licensed population of imlifidase. The ERG's suggested patient group is therefore inappropriate for use as a comparator as it includes patients outside the marketing authorisation. The appropriate comparator within this appraisal is standard of care for patients within the market authorisation of imlifidase. UK clinical expert opinion expressed to Hansa* is that this will be dialysis for all patients, with only a very small minority potentially not on dialysis initially and these patients would rapidly

* For the preparation of this response document, Hansa has consulted with Dr Adnan Sharif, Consultant Nephrologist, Queen Elizabeth Hospital, Birmingham and Dr Rommel Ravanan, Consultant Nephrologist, North Bristol NHS Trust.

		need to start dialysis (within a maximum of 6 months of being placed on the transplant list). The ERG makes reference to the opportunity cost within this appraisal; however, the ERG did not consider the other side of this, which is the cost of inaction for those patients who could receive imlifidase. As imlifidase allows transplant to occur in patients who would otherwise be unlikely to receive a transplant, the cost to these patients of inaction is likely to be a significant wait before transplant whilst their health deteriorates, leading to a higher likelihood of a less favourable outcome to their eventual transplant (as shown in a French study where graft survival rates declined with comparatively longer periods of dialysis before transplant; Prezelin-Reydit M, et al. Nephrol Dial Transplant 2019; 34: 538–545) or, for many of these patients, no transplant at all as they become too sick to receive a transplant whilst waiting. Therefore, the cost and burden of inaction to these patients is very high. Hansa also believes that when considered at the population level, the small numbers of imlifidase patients would make no significant impact to the average wait time for transplant but would simply act to reduce the variance around the average waiting time by greatly reducing the waiting time of a relatively small number of patients (in fact allowing a transplant to occur when one would not otherwise take place).
Key issue 2: Placement of imlifidase in the UK treatment pathway	**No**	This key issue includes many factors that have already been discussed within the response to Key Issue 1, particularly regarding the interaction between the KOS and imlifidase. Hansa believes that considerations of changes to the KOS are beyond the scope of a NICE appraisal, and therefore beyond the remit of this appraisal. Hansa also believes that when imlifidase is used in line with its licence (for the small number of patients who do not benefit from the KOS), there should be no necessity to alter the KOS in the short term to accommodate its use (this view was supported by UK clinical experts*). The licence for imlifidase clearly states that imlifidase should be considered for patients who remain unlikely to be transplanted under available schemes (the KOS

* For the preparation of this response document, Hansa has consulted with Dr Adnan Sharif, Consultant Nephrologist, Queen Elizabeth Hospital, Birmingham and Dr Rommel Ravanan, Consultant Nephrologist, North Bristol NHS Trust.

		being the main relevant scheme within the UK). Therefore, imlifidase is a treatment applicable to a targeted small cohort of highly sensitised patients who do not currently benefit from the KOS (Hansa estimates that there is a total imlifidase eligible population in the UK of 113 patients, which will equate to a maximum of 25-35 imlifidase patients per year). Imlifidase is acting to allow transplant to occur only in this small group of patients, and this view was supported by UK clinical experts consulted by Hansa*. The introduction of imlifidase would therefore allow the intentions of the KOS (in terms of equalising access to transplant for highly sensitised patients) to be more fully realised for patients who do not receive the currently intended benefits of the KOS due to their level of sensitisation and immunological profile. Therefore, given these facts, any impact to the KOS from the introduction of imlifidase can be expected to be minimal. Hansa agrees with the ERG that the practicalities of the use of imlifidase and associated treatment protocols still need to be fully decided within a UK setting. Hansa has become aware that a number of KOLs have indicated that a "UK unified approach" (potentially including use and pre-identification of suitable candidates, immunologic risk profile, pre- and post-transplant immunosuppression and safety monitoring based on trial designs as a framework) developed by a working group of UK experts would be a suitable way forward. Hansa also wishes to point out that the clinical trial data available for imlifidase were collected across multiple countries with some variation in clinical practice between them. Hansa therefore believes that this demonstrates that imlifidase can successfully fit within different treatment protocols. Hansa believes the practicalities of ensuring imlifidase fits into UK protocols are best informed by clinicians. The ERG express concerns around the time of action for imlifidase treatment. Hansa noted that the SmPC includes the following statement, "*PKPD modelling showed that at 2 hours after administration of 0.25 mg/kg imlifidase, a crossmatch test is likely to become negative in 96% of the patients, and after 6 hours at least 99.5% of the patients are likely to become crossmatch test negative*." Therefore,

* For the preparation of this response document, Hansa has consulted with Dr Adnan Sharif, Consultant Nephrologist, Queen Elizabeth Hospital, Birmingham and Dr Rommel Ravanan, Consultant Nephrologist, North Bristol NHS Trust.

		the time of action required is 2 hours for almost all patients. Hansa also wishes to clarify that the time at which the lowest donor specific antibody (DSA) values occur does not provide a representation of when conversion to negative crossmatch may have occurred, as was implied by the ERG within its report. With respect to cold ischemia time, the clinical studies showed a considerable variation, that was to a large extent related to transport distances and logistics (much longer CITs were observed in the US clinical trial patients). Although some impact on CIT cannot be ruled out, taking into account the rapid action of imlifidase, this treatment is not anticipated to have a major impact on the CIT.
Key issue 3: Generalisability of the evidence to NHS contexts	**No**	Hansa has confidence that the available clinical trial evidence can be considered to be generalisable to the NHS context. Hansa is aware that there are some differences between kidney allocation schemes and priority schemes between countries, and that there are also some differences in treatment protocols. However, the underlying biology remains consistent and so the generalisability of the data across countries can reasonably be assumed. Hansa has received UK clinical expert support of this position and of the generalisability of the clinical evidence to the NHS context*. Hansa notes again that imlifidase is a product developed for an orphan indication under the EMA PRIME scheme. This recognises that an unmet medical need exists in the imlifidase patient population. Imlifidase has been granted a Conditional Marketing Authorisation by EMA on the basis of this unmet need. A Conditional Marketing Authorisation is approved, "…*where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required*…". The clinical evidence for imlifidase met these requirements and was sufficient for the granting of the Conditional Marketing Authorisation. The evidence currently available for imlifidase is therefore limited for the treatment of this orphan condition. Hansa has presented all data that are currently available and additional studies are ongoing (as mandated by the terms of the Conditional Marketing Authorisation). Hansa also notes that the clinical trials for imlifidase were conducted across multiple countries with some differences in protocols. Despite

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		this, there were no significant differences seen across primary outcomes. This provides confidence that the results can be considered generalisable to the UK. The ERG asserts that efficacy "…*relies on the implicit assumption that absent the drug, specific outcomes (such as negative crossmatch tests) would not have been observed*." Hansa again notes that for a patient with a positive crossmatch test there is no known biological process or reason that this would rapidly convert to a negative crossmatch. The ERG also states that a matched comparison would be desirable additional evidence. However, such an analysis has not been conducted and Hansa has not identified any literature to inform a matched comparison within the indicated population for imlifidase. This is due, as the ERG notes, to this indication being a new, very small population within this area that has not been extensively studied.
Key issue 4: Interpretation of treatment outcomes following transplant	**No**	Many of the relevant points in response to this Key Issue match those above for Key Issue 3. The main point being that imlifidase is a product developed for an orphan indication under the EMA PRIME scheme and has been granted a Conditional Marketing Authorisation. Hansa recognises that this has been granted in an orphan indication and therefore somewhat limited data are available for this product. EMA guidance states that a Conditional Marketing Authorisation is approved, "…*where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required*…". Imlifidase met these requirements and the clinical evidence available was sufficient for the granting of the Conditional Marketing Authorisation. All available evidence has been presented to NICE and further data collection with regard to the outcomes following transplant are ongoing, as mandated within the Conditional Marketing Authorisation. Furthermore, additional data from several of the trial outcomes were used as input to a robust and validated graft survival prediction algorithm (iBox, which has been developed by the Paris Transplant Group; Loupy A, et al. BMJ 2019; 366: l4923). It is rare that, at launch, studies on an orphan product can generate this type of advanced data and such a robust prediction of long-term efficacy. The long-term efficacy outcome prediction made through iBox ensures that there is more robust economic modelling with less

		uncertainty for imlifidase, when compared to the equivalent data that are normally available for orphan products at their launch.
Key issue 5: Comprehensiveness of the clinical evidence base	**No**	The ERG provides criticism of the data available for the target population. Hansa notes that the target population is the same as the licensed population. Furthermore, the EMA found that the data presented for this group were sufficient to demonstrate the safety and efficacy of imlifidase and allowed the granting of the Conditional Marketing Authorisation. Hansa therefore believes that the evidence base available is sufficient to demonstrate the efficacy and safety of imlifidase within the licensed population. The ERG requested further clarification and re-presentation of some aspects of the clinical data, particularly with regard to the primary study endpoint of crossmatch conversion. Hansa believes that the summary of clinical efficacy produced by the ERG as Appendix B to its report provides a full and accurate picture of the available clinical data within the most relevant patient population. Hansa would also like to provide some further clarity on the measurement of crossmatch conversion to explain some of the omissions noted by the ERG (for example on timepoint of measurement). The trial protocols included crossmatch tests at 2 hours, 6 hours and 24 hours (Study 03 also included a test at 1 hour) post-dosing of imlifidase. However, due to clinical considerations, and the need for transplant to proceed in a timely manner, when a negative crossmatch test was received further tests were generally not conducted. The primary endpoint was concerned with crossmatch conversion before transplant and not the exact timing of this outcome, and so these data have been presented without information of the timepoint as there will have been some variation in this between different patients. Hansa does not have any additional data available to present around this at this time. However, the SmPC includes the following statement, "*PKPD modelling showed that at 2 hours after administration of 0.25 mg/kg imlifidase, a crossmatch test is likely to become negative in 96% of the patients, and after 6 hours at least 99.5% of the patients are likely to become crossmatch test negative*." This shows that in the majority of cases this crossmatch conversion will have occurred at 2 hours. Additionally, the ERG noted difficulties in tracking which crossmatch tests were used. The specific crossmatch tests used were defined by each centre's standard protocols, so as to minimise interference with the transplant process.

		Hansa notes that since flow crossmatch testing is more sensitive than CDC crossmatch testing, a negative flow crossmatch was in many cases taken to imply a negative CDC crossmatch test (and a CDC crossmatch was not always therefore undertaken). Also, as mentioned above, once a negative crossmatch was achieved, further crossmatch tests were not conducted. These factors cause the number of tests reported to vary in some cases and Hansa believes this may be the root of some of this confusion. The ERG also requested presentation of all scoped outcomes, Hansa wishes to make clear again that all available data related to the scoped outcomes has been presented to NICE and no additional data are available in that regard.
Key issue 6: Comparators in the economic model	**No**	The first major factor in relation to this Key Issue is the same point related to comparators outlined in the response to Key Issue 1. The scope for this assessment is within the marketing authorisation of imlifidase, and so the relevant comparator is standard of care for patients within the market authorisation of imlifidase. The comparator outlined by the ERG does not match the licensed indication of imlifidase, and hence the scope. In particular, the data that the ERG has procured from NHSBT do not represent the target population of imlifidase, and, furthermore, Hansa does not believe that they represent a group that falls within the licensed indication. Whilst Hansa are grateful to the ERG for attempting to gather relevant data on the target population, unfortunately this has not been achieved. The data utilised by the ERG is stated to be a group of very highly sensitised patients, with a cRF of ≥99%. Hansa notes that no substantial justification is given for the choice of this value and no reference is made to any engagement with clinical experts about the choice of this value. However, as proven by the data on this group, it cannot be considered to only consist of a group of patients who are "*…unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.*" as is required by the licence of imlifidase. This is clearly highlighted by the ERG reporting that this group had an annual transplant probability of 17.2%, and hence the entirety of this group clearly cannot be considered unlikely to be transplanted. Hansa believes, as the ERG allude to

		briefly, and has been relayed to Hansa by clinical experts*, the majority of transplants in this very highly sensitised group will occur within the first 18-24 months of these patients entering onto the transplant waiting list. These transplants are not just a factor of luck but are due to the immunological profile of these patients and the availability of suitable living donors for some patients, showing that this overall group cannot be considered as the imlifidase eligible population. Hansa also notes that the practice of early (pre-emptive) listing of patients has increased in prevalence in recent years, particularly amongst highly sensitised patients (which is likely to account for the patients not on dialysis identified by the ERG). This often includes patients at a point before they require dialysis and is done to maximise the ability of patients to receive a timely transplant and provide the greatest opportunity for the best transplant outcomes. Hansa does not believe that pre-emptively transplanted patients form part of the imlifidase target population (or the licence of this treatment). Hansa intends (and the licence requires) that imlifidase should be reserved for patients who are unlikely to get a transplant after all other considerations (such as the KOS) have been made, in line with the licence for this product. As outlined above, Hansa believes that the figures used by the ERG for transplant within the comparator population are not correct (the ERG have derived a model input of 31.4% for transplant rate in comparator patients [this is the annualised rate of 17.2% applied over a two-year period where patients were judged by the ERG to remain in suitable health for a transplant]). The main concern being that the figures derived by the ERG are from a population that is not “unlikely to be transplanted” and hence does not match the license of imlifidase; with many of the transplants recorded in this group being likely to occur for predictable reasons such as the availability of a living donor or the patient has an immunological profile that is not particularly problematic. However, Hansa does accept the point from the ERG that unlikely to be transplanted does not mean that there is no chance of

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		transplant. By definition, these patients are unlikely to be transplanted and so this value would be expected to be very low. Hansa does not have additional data on which to base this estimation currently, however, a better clinical definition of this group may allow more appropriate data to be gathered from NHSBT. UK clinical expert opinion received by Hansa* has indicated that this figure would be very low, and so Hansa has utilised a figure of 1% of imlifidase eligible patients in the updated company base case. It is important not to overlook the fact that the decision to transplant with the use of imlifidase is a highly individualised decision based on many factors, which enable this treatment to be targeted at patients that are unlikely to ever receive an HLA-compatible organ offer through the current systems. Hansa disagrees with the ERG's choice of relevant comparators for this appraisal. The ERG states that the analysis does not match the NICE scope as it does not compare imlifidase versus clinical management without imlifidase. However, this fails to consider the imlifidase licence in relation to the NICE scope. The scope was produced before the granting of the Conditional Marketing Authorisation for imlifidase and so was deliberately left broad by NICE. Hansa has conducted an analysis in line with the NICE scope but also in line with the licence for imlifidase. However, the ERG analysis does not match both the scope and the licence. The ERG consider the wider scope but do not recognise that the imlifidase licence only represent a subgroup of these patients. The relevant comparison for this appraisal is imlifidase treated patients versus those same patients receiving clinical management without imlifidase. Hansa believes strongly that clinical management without imlifidase should be considered to be dialysis. Imlifidase is intended as a treatment to allow transplant to occur in patients who have exhausted all other options and remain unlikely to receive a transplant. This would be unlikely to include patients who are pre-dialysis and being pre-emptively transplanted, as these patients are at the start of renal replacement therapy and likely to have other options open to them at this time. A

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		clear illustration of this is that within the clinical trials of imlifidase all patients had been receiving dialysis before transplant, on average for over seven years. UK clinical expert opinion expressed to Hansa* is that the treatment for the relevant group of patients without imlifidase would be dialysis for all, with only a very small minority potentially not on dialysis initially and these patients would rapidly need to start dialysis (within 6 months of being placed on the transplant list). Hansa accepts that accounting for all patients receiving dosing of imlifidase may be considered more appropriate for modelling. Hansa had not accounted for this factor as it was expected that the rate of dosing where a transplant was not able to occur is very low. However, Hansa accepts that in the absence of better data the figures from the clinical trials are most appropriate source currently available for this data. Hansa considers whether transplant successfully occurred is the relevant factor for the economic modelling (and this is also the most relevant clinical outcome). Hansa notes that the one patient who did not achieve a full crossmatch conversion within the trial had a borderline flow crossmatch and negative virtual crossmatch following imlifidase. Whilst from an analytical standpoint this could not be considered a full crossmatch conversion, within the time critical situation for transplant, this result was judged as not clinically significant and the transplant was successfully carried out. Given this fact, Hansa finds the most appropriate figures to use are those related to imlifidase treated patients who did not receive a transplant. Hansa also believes that the patients in Study 02 should not be included in this consideration as this study did not have the outcome of transplant as a defined part of its protocol, and, as noted by the ERG, transplant was 'incidental' within this study. From these figures 45 of 46 patients treated with imlifidase successfully received a transplant (97.9%). Hansa believes that this is the most appropriate figure to use within the economic model.

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		Whilst Hansa accepts that some of the analyses conducted by the ERG are constrained by the model structure, Hansa believes that the analysis by the ERG including transplant within the comparator group also fails to take account of discounting of future costs/benefits, which makes this analysis overstate the benefits within the comparator group. By definition these patients are unlikely to receive a transplant and without imlifidase there is likely to be a significant delay before a suitable organ is available for these patients. The approach taken by the ERG does not provide any acknowledgement of the benefits that imlifidase provides by enabling a timely transplant compared to a significantly delayed transplant (there is also no available data to quantify the potential extent of this delay). The ERG's approach to this modelling also does not account for the significant upfront dialysis costs that would be experienced by these patients before their transplant could occur. The model is also not (due to a lack of available data) able to model the decline in health that occurs on dialysis and factors such as the loss of hope that may occur in patients who become too ill to remain on the transplant list. All of these factors lead the ERG's analysis in this area to significantly overestimate the ICER value and underestimate the benefits of imlifidase.
Key issue 7: Quality of life data used in the economic model	**No**	Hansa gratefully recognises the work that the ERG has done to identify a recent and relevant publication in relation to utilities. Hansa wishes to note the lack of published data in this area and restate that the utilities used in the company submission were judged to be the most appropriate given what was available at the time of submission. Hansa does, however, retain some concerns around the utilities chosen by the ERG and the values within Cooper et al. that the ERG considered most appropriate. This issue returns to the considerations of Key Issue 1 and Key Issue 6, and to the question of the relevant comparator in this appraisal. Hansa strongly believes that the comparator group within this appraisal will consist of patients on dialysis (as confirmed by expert opinion*), and therefore the relevance of a general pre-transplant population is unclear. The data utilised by the ERG are stated to

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		utilise the longitudinal data reported within Cooper et al. and Hansa believes that these are therefore derived from only a single publication by Ortega T et al. (Transplantation 2007; 84(11): 1428–1435). On closer inspection of this primary reference, it is unclear as to the exact characteristics of the study population and they appear to be a general transplant population. This raises questions of the applicability of this data to the UK and the population of interest in this appraisal. Spain is a world-leading country in kidney transplantation, with a high availability of deceased donor organs and where patients are transplanted after 8 months on average (https://www.txmultilisting.com/waiting-times-worldwide.htm), which compares to a median time (for all patients) on the waitlist in the UK of 633 days (NHS Blood and Transplant. Organ Donation and Transplantation Activity Report 2019/20. 2020). The patients in the Spanish study represent a general pre-transplant population, which is likely to include a proportion of pre-emptively transplanted patients who are pre-dialysis or who have been on dialysis for limited time periods. The utilities are likely to be substantially higher for this group of patients than for those who have been on dialysis for many years (as is case for the imlifidase population, who in the clinical trials had, on average, been on dialysis for over seven years). This is an important consideration for the model, as the dialysis health state represents many patients who have already been on long-term dialysis and who remain on dialysis for the lifetime of this model. The long-term health impacts of dialysis are well known, with increasing risk of adverse events (such as stroke) over time (Findlay M, et al. Nephrol Dial Transplant 2018; 33(9): 1564–1571) that leads to an increased mortality for patients on dialysis (UK Renal Registry. UK Renal Registry 21st Annual Report – Data to 31/12/2017. 2019). The utilities derived from a general pre-transplant population are likely to be substantially higher than those seen by patients who have spent many years on dialysis and potentially have no chance of receiving a transplant which would lead to a loss of hope and other mental impacts likely to reduce utilities further. Therefore, using a pre-transplant population (who may not be on dialysis) cannot be considered representative of the modelled patient population. The population considered within this Spanish study is also self-selecting, as it only includes a consideration of those patients who ended up receiving a

		transplant. This therefore means that it includes only patients who ended up receiving a transplant and will have directly excluded many of the patients most relevant to this appraisal, those with a very low chance of transplant. The mental state of these patients, who will have had a high expectation of transplant, will be very different to those who have been several years on the waitlist and have great uncertainty if they will ever be transplanted. The decrements in utility due to anxiety, depression and these other mental impacts will not be reflected in this study of Spanish patients. Overall, Hansa therefore believes that dialysis-specific utilities would be more representative of the patient population required for this appraisal, and the modelled patient population throughout the time horizon of the model. Given these facts, Hansa feels that the Liem et al. publication used in the company base case contains the most appropriate available data (as this meta-analysis focussed on a general dialysis population, with a broad mix of patients including those on long-term dialysis). Hansa would also like to state that quality of life data are currently being collected within the long-term follow-up study of the imlifidase trials (17-HMedIdeS-14), and similar data are also being collected within post-approval studies. However, at this time, no data are currently available for quality of life within imlifidase treated patients. Hansa notes that the model does not incorporate certain factors associated with long-term dialysis and removal from the transplant list on utility. Mental health issues such as depression or a loss of hope when a transplant is no longer an option for a patient are likely to have a significant impact on utility, however it has not been possible to source data to allow for the inclusion of these factors within the model. These factors are likely to decrease the QALYs in the comparator group and hence reduce the ICER value for imlifidase.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Imlifidase patient population	**Sections 2.2, 2.3, 2.4, 3.2, 3.6, 4.2, 6.1, 6.2, 6.3, 6.4, 6.5**	**No**	The licence for imlifidase defines the relevant patient group eligible for this treatment. Hansa intends that the population of interest for this appraisal covers the whole licensed population. A correct interpretation of the licence of imlifidase and subsequent definition of the eligible patient population is important for this appraisal as this issue impacts or resolves a number of the Key Issues identified by the ERG. The licence for imlifidase states "*Idefirix [imlifidase] is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix [imlifidase] should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.*" From the licence, Hansa included within the Company Submission a summarised version of the criteria for defining the imlifidase eligible patient population. This was that imlifidase should be available as a treatment option for adults with CKD awaiting a kidney transplant from an available deceased donor, if: • The transplant recipient is highly sensitised (cRF ≥85%), and • There is positive crossmatch against the donor kidney, and

			• The patient remains unlikely to be transplanted, despite the revised KOS, and • The transplant has an acceptable risk profile for the recipient. From the ERG report, it is clear that further consideration is required as to the definition of unlikely to be transplanted. A clear definition of this factor will help define this patient group clearly within this appraisal. The ERG has not accurately presented the definition of unlikely to be transplanted patients, and in some cases has also misrepresented Hansa's position in this regard. The ERG has made numerous assertations that Hansa has defined unlikely to be transplanted patients as having ≥95% cRF and positive crossmatch. This definition was used to define the subgroup within the pooled analysis conducted to provide the most supportive evidence. As noted on page 77 of the Company Submission, "*The criteria chosen for this analysis were not tied to any particular guideline or specific clinical practice, and were used purely to define a population for regulatory analysis which is similar to the expected European patient population*." This definition was chosen as a means of selecting the most relevant patients (in relation to the licence) from within the total clinical trial population. This analysis group was derived from the available clinical trial patients to be representative of the licensed population of imlifidase, and was also derived with the aim of providing a dataset that could be used as a tool for discussion across different European countries with different KOS/priority access schemes. Hansa has never tried to define the imlifidase target population based solely on cRF/cPRA levels. Hansa does not believe that arbitrary cut-offs in cRF values can be used to accurately define imlifidase eligible patients. Hansa believes that the

			decision as to which patients remain unlikely to be transplanted is best determined by the treating physician as this is a complex determination that cannot be linked to cRF/cPRA values alone and is determined by the specific immunological profile of a patient. This view has been supported by clinical experts consulted by Hansa* and the ERG (ERG report page 24). As noted within the company submission, Hansa believes that a small number of imlifidase eligible patients will fall within the cRF range of 85-95% due to their particular immunological profile. A strict definition of unlikely to be transplanted based on cRF alone would not be able to capture these patients and would therefore further marginalise this already disadvantaged group. Within the ERG report, the ERG considers data that they have acquired from NHSBT. These data are presented as an analysis of patients with a cRF ≥99% and are subsequently used within the economic modelling conducted by the ERG. However, this provides a good example of how cRF alone cannot define a group of patients as unlikely to be transplanted. The ERG reports on page 89 that the annual transplant probability is 17.2% in these patients with a cRF ≥99%. This clearly illustrates how a significant minority of these patients are receiving a benefit from the KOS and receiving a timely transplant, but these patients, therefore, cannot be considered to be unlikely to be transplanted (and therefore within the licence of imlifidase). On the same page, the ERG note that the majority of these transplants occur soon after entry onto the waiting list, and expert opinion provided to

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			Hansa* is that this would be within around 18-24 months. This leads to the potential that a requirement to have been on the waiting list/dialysis for a defined period of time may be a means of helping to define highly sensitised patients who are unlikely to be transplanted. Expert opinion (as reported to Hansa* and also noted by the ERG on page 24 of their report) is that the target patients for imlifidase are clinically distinct and can be recognised by skilled experts within around two years of being on the transplant list. However, providing simple criteria to define these patients is extremely difficult. Hansa does not wish for imlifidase to be used outside its license and believes that clinical expert input in this area is essential to identify the best definitions possible that will allow suitable patients to be identified. Expert opinion expressed to Hansa* is that tight restrictions on the patient population are not appropriate as clinical judgement is needed so that clinicians have flexibility to prescribe imlifidase to the few relevant patients. The application of clinical judgement would also avoid eligible patients being denied treatment because they do not fit a set of strict criteria that in some cases would not be entirely appropriate. Further consultation with clinicians and relevant expert groups in this area would be of great value in helping to produce a workable definition of this patient group. The consultation that Hansa has conducted with clinical experts* has led to the following factors being identified as a potential framework for defining the imlifidase patient population:

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			• Patient is at high immunological risk. DSA profile shows low chance of receiving transplant by other means (e.g. including, but not limited to, matched offer including after delisting antigens), or patient has a high level of urgency for rapid transplant (for example due to imminent loss of vascular access), and • Expected long wait time on dialysis (this could be expressed as predicted wait time for transplant [for example using NHSBT tool]), and • Only alternative option available would be HLA-incompatible transplant, and • DSA elimination to transplant at permissible levels not possible by any other means, and • ABO compatible, and • Not used in patients requiring combined transplants (such as kidney/pancreas). Hansa believes that it may be most appropriate to restrict use of this highly specialist treatment to a small number of 'centres of excellence' where the specific knowledge and experience is available. Hansa also believes that maintaining physician discretion is important to allow imlifidase to be targeted at the most appropriate patients. Whilst Hansa wishes to avoid strict and inflexible criteria being imposed, Hansa is not averse to a set of well designed, flexible and clinically relevant criteria being applied to imlifidase patient identification; especially where clinical judgement is preserved within the system.
Additional issue 2: Equality	**Section 2.4**	**No**	The ERG provides almost no comment on the equality considerations raised by this appraisal. These issues were outlined within Section B.1.4 of the Company Submission, and Hansa believes that they are an important aspect that should be properly considered by the committee.

			Briefly, people who are highly sensitised are currently not being provided the same access to kidney transplantation or standard of care as those who are non-sensitised. The average waiting times for highly sensitised patients is over double that of non-sensitised patients (Pruthi R, et al. Nephron Clin Pract 2013; 125(1–4): 81–9), with the most disadvantaged patients having even longer waiting times (if a transplant is able to occur at all). While the recent updates to the UK KOS have aimed to reduce some of this inequality in access to transplant, there remain particular groups where access to transplant remains restricted and where this inequality has not been addressed by the updated KOS. The impact of this disadvantage is severe as it prevents these patients receiving the current gold standard of kidney transplant and leaves them likely to need many years of dialysis, which is a highly burdensome treatment. This disadvantage is particularly pronounced for potential imlifidase patients, as they are unlikely to be able to ever receive a transplant. Certain protected groups remain at a particular disadvantage in regard to transplantation, which are the female population and BAME populations. Pregnancy is one of the most common causes for a patient to become sensitised with anti-HLA antibodies, and so there are more women within the highly sensitised group, and a disproportionate number of women waiting longer for a transplant. BAME groups also experience disadvantages in relation to access to transplant and are disproportionally represented on the kidney transplant waiting list and have longer average wait times. This is a complex issue that has numerous causes, but sensitisation is one aspect of this, with data showing that there are higher matchability scores within black patients (Williams A, et al. Exp Clin Transplant. 2018;16(6): 682–689). Imlifidase can

			help to increase access to transplant for highly sensitised patients, and the disproportionate presence of the above protected groups within highly sensitised patients means that the use of imlifidase may help to equalise access to the current gold standard treatment of transplant. From the clinical trial results to date, there is no evidence of any difference in efficacy of imlifidase within these protected populations. However, the inability to receive a transplant is associated with worse quality of life, worse health, worse outcomes and a higher mortality rate. For example, the graft survival rates following transplant have been shown to be more favourable with comparatively reduced pretransplant dialysis duration in a French study (Prezelin-Reydit M, et al. Nephrol Dial Transplant 2019; 34: 538–545). It is also clear that the overall benefit from transplant remains even for transplants that occur after long periods on dialysis (Life year gains presented within Gill JS, et al. Kidney Int 2005; 68(5): 2345–2351). The main explanation for these improved benefits from transplants with reduced time on dialysis are due to the long-term negative health impacts of dialysis, which are well known. There is an increased risk of many adverse events (such as stroke) over time (Findlay M, et al. Nephrol Dial Transplant 2018; 33(9): 1564–1571) and an increased rate of mortality for patients on dialysis (UK Renal Registry. UK Renal Registry 21st Annual Report – Data to 31/12/2017. 2019). Furthermore, the full costs and utility impacts of adverse events (and declining health) which occur over long-term dialysis are not fully captured within the economic model (due a lack of usable data on these issues). This will lead to an overestimation of ICER values for imlifidase within the model.

Additional issue 3: ERG preferred modelling assumptions	**Section 6.1, 6.2, 6.3, 6.4**	**No**	Hansa wishes to provide a reply to each of the ERG changes made to the economic model to provide clarity on these and to outline the details behind the updated company base case outlined below. Corrections to model – Hansa accepts all four ERG error fixes (0-6 month transplant costs, imlifidase and transplant adverse events, caregiver disutilities, transplant adverse event costs). Change 1 (Rate of transplant in imlifidase treated patients) – Hansa accepts that accounting for all patients receiving dosing of imlifidase may be considered more appropriate for modelling. It is expected that in clinical practice at the population level, that the rate of transplant will be very close to 100%. However, given the current available data, the clinical trial data is the only available source to derive this figure from. Within the clinical trial data, Hansa considers that the most appropriate figures to use are those related to imlifidase treated patients who did not receive a transplant. Hansa also believes that the patients in Study 02 should not be included in this consideration as this study did not have the outcome of transplant as an essential part of its protocol (although transplant was allowed by the protocol if the opportunity arose), and as noted by the ERG transplant was 'incidental' within this study. From these figures, 45 of 46 patients treated with imlifidase successfully received a transplant (97.9%). Hansa have used this figure for the updated company base case. Change 2 (Rate of transplant in comparator group) – Hansa accepts the ERG's point that this value is likely to be above 0%; however, Hansa has major issues with the value proposed by the ERG (and this relates to the factors discussed in Additional Issue 1 and Key Issue 6). The ERG

			figures derived from NHSBT data do not match the imlifidase target population and is likely to include a substantial group of patients that fall outside the licence for imlifidase. In the absence of any alternative data being available at the current time, Hansa has relied on UK clinical expert opinion* that has indicated that for the imlifidase population of unlikely to be transplanted patients, that transplant would occur for only a very minimal proportion. Hansa has therefore used a figure of 1% for this input in the updated company base case. Change 3 (No dialysis as an option for comparator group) – This input and the related issues are discussed in Additional Issue 1 and Key Issue 6. Hansa strongly believes that when using the relevant comparator group, this patient group will all be on dialysis (or will imminently start dialysis). This view has been confirmed by clinical experts*. Hansa also has noted an issue in the analysis as implemented by the ERG. In the ERG report (Section 6.3.3, page 90), it is stated that "*The ERG understand it is likely that all patients may receive dialysis at some point however, particularly as patients age. It is therefore assumed that after the first two years, all patients will move to dialysis in the ratio seen in the NHSBT data.*" Upon inspection of the ERG updated clinical model, Hansa notes that this intention is correctly encoded within the 'Markov dialysis' worksheet to model the patient flow through an additional health state, and no cost of dialysis is applied to the patients within this health state. However, the changes in this area have also been incorrectly applied to the cost of dialysis across the whole model. The ERG have updated the proportions of patients receiving each type of

* For the preparation of this response document, Hansa has consulted with Dr Adnan Sharif, Consultant Nephrologist, Queen Elizabeth Hospital, Birmingham and Dr Rommel Ravanan, Consultant Nephrologist, North Bristol NHS Trust.

			dialysis and have incorporated these changes into the 'Costs' worksheet, which influences the cost of dialysis per cycle calculation. In doing so, the ERG has not accounted for their addition of patients not receiving dialysis. This therefore means that the cost of dialysis under this ERG modification is artificially reduced for all dialysis patients across the entire model. This is a severe flaw in this scenario and has two underlying components (that Hansa has identified): the split between haemodialysis (HD) and peritoneal dialysis (PD); and the split between subtypes of HD. Both these splits should combine to cover 100% of patients within the cost calculations, as this calculation is for cost for patients on dialysis and therefore by definition all patients in this calculation are receiving dialysis. The HD/PD split does not account for the proportion of patients that the ERG assigned to not receive transplant. Whilst the split between hospital, satellite and home HD has also been incorrectly coded to not account for these three modalities forming the totality of HD patients, and instead considers the proportion of these modalities out of the total dialysis population (including those not on dialysis). This leads to 25.5% of HD patients being assigned no costs, and this can be verified easily from a quick check within the 'Costs' worksheet where the total cost for HD under this ERG assumption is calculated to be less than the individual cost of the cheapest subtype of HD (satellite HD), and this is even with the other dialysis costs (transport, erythropoietin stimulating agents, access costs and nephrologist visits) being included in the total HD cost. Under the company base case assumptions the per cycle dialysis cost was calculated to be £16,803, whereas under this ERG scenario it was reduced to £13,812. However, when the coding of the proportions is corrected within the ERG scenario the cost per cycle of dialysis should actually be £17,301 under the ERG's base case assumptions.

			Hansa has not updated the company base case in respect to this point, and notes that the dialysis costs in the company base case are below those estimated using the ERG's updated figures. Change 4 (Updated utility source) – This issue is discussed as Key Issue 7. There is continued uncertainty in this appraisal as to the relevant comparator, which has the impact of making the relevant utilities for this group unclear. Hansa strongly believes that dialysis patients are the relevant comparator group as supported by expert opinion*, and that the utilities from Cooper et al. used by the ERG do not reflect this group. Therefore, at the current time Hansa has not made any changes to the company base case.
			Change 5 (Updated carer disutility source) – Hansa were aware of the shortcomings of the identified disutility data source. Hansa is pleased to accept the more UK-relevant data identified by the ERG as part of the updated company base case. Change 6 (Apply carer disutility to 90% of HD patients) – Hansa accepts that this is a reasonable change to the model and has included this change in the updated company base case. Change 7 (Redistribute hospital transport types) – Hansa challenges the ERG's approach to this issue. The ERG identifies concerns related to the cost of hospital transport related to the age of the identified source. However, the

* For the preparation of this response document, Hansa has consulted with Dr Adnan Sharif, Consultant Nephrologist, Queen Elizabeth Hospital, Birmingham and Dr Rommel Ravanan, Consultant Nephrologist, North Bristol NHS Trust.

			ERG's solution to this issue was to disregard the costs for one category of transport costs without identification of any more relevant evidence in this area. Hansa does not believe that a blanket disregard of these patients and the assumption that these would be distributed evenly across the other transport options to be a reliable assumption as no particular justification is given by the ERG for this approach. Hansa believes that in the absence of any other evidence, the available figures should be used and not artificially altered. Therefore, Hansa has not included this change within the updated company base case. Change 8 (Add cost of one crossmatch test after each dose of imlifidase) – Hansa had assumed that the costs of crossmatch tests would be incorporated within the costs of transplant, as these tests would already be conducted in routine clinical practice. Hansa accepts that a consideration of the potential increase in costs associated with additional crossmatch tests is a justifiable inclusion into the model. Hansa notes that the ERG approach has the potential to overestimate the cost of imlifidase if routine crossmatch tests are already conducted before transplant. Hansa has included this consideration within the updated company base case. Change 9 (Use clinical trial patient weight throughout model) – Hansa accepts this logical change to the model. Change 10 (Include DSA test costs in model) – Hansa had assumed that DSA tests would occur at graft loss and be incorporated into the cost of this event. Hansa is happy with the ERG's approach to these costs and have included this in the updated company base case.

			Hansa would also like to note that there remain costs and benefits not captured within the economic model. Many of these relate to the adverse events and related costs of long-term dialysis, but also includes the benefit from immediate transplant with imlifidase compared to an extended wait and the utility impact of the mental aspect associated with long term dialysis (including a loss of hope associated with removal from the transplant list due to declining health). These areas would, if captured, all act to reduce the ICER associated within imlifidase. Hansa also has concerns that the ERG has conducted analysis that appear to consider factors in one direction only and thus artificially raise the ICER for imlifidase; this concern is particularly amplified by the error made by the ERG that has a substantial impact on artificially reducing the costs of dialysis in the model. In these cases, Hansa believes a fair and more balanced approach is needed that considers fully the costs and benefits associated with imlifidase and comparators. Given the uncertainty in this appraisal related to the population of interest and relevant comparator, Hansa have not been able to commit to any revisions to the submitted patient access scheme at this time.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Additional Issue 3	-	Errors corrections applied by ERG are accepted by Hansa	£31,971 (+£1,330)
Additional Issue 3	Carer disutility derived from Nagasawa et al. publication	Carer disutility source updated to Thomas et al. to match ERG preference	£31,431 (-£541)
Additional Issue 3	Carer disutility applied to all HD patients	Reduce the proportion of HD patients with a carer to 90% to match ERG preference	£32,009 (+£38)
Additional Issue 3	Cost of crossmatch tests assumed to be covered within reference costs	Include one crossmatch test after each full dose of imlifidase to match ERG preference	£32,049 (+£78)
Additional Issue 3	Average patient weight for maintenance immunosuppressive therapy cost set to 75kg	Change average patient weight to 69kg to match ERG preference	£31,942 (-£29)
Additional Issue 3	DSA test costs were assumed to occur at graft loss and be included within the costs incurred at this point	Apply cost of DSA tests for three separate antigens once per year, and additionally to occur once at graft loss to match ERG preference	£32,344 (+£373)
Key Issue 6/ Additional Issue 3	All patients who receive imlifidase assumed to proceed to transplant	Assumption updated for transplant following imlifidase to occur for 97.9% (45/46) of treated patients	£33,409 (+£2,768)
Key Issue 6/ Additional Issue 3	Comparator patients assumed not to be able to receive a transplant	Comparator patients assumed to have very low rate of transplant (1%)	£32,254 (+£1,613)

Company's preferred base case following technical engagement	**Incremental QALYs: [redacted] Commercial in confidence information removed**	**Incremental costs: [redacted] Commercial in confidence information removed**	**£33,658 (+£3,017)**

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Monday 1 March 2021**.

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.

PART 1 – Living with or caring for a patient with chronic kidney disease who is highly sensitised and current treatment options	
About you	
1.Your name	**Richard Ayres**
2. Are you (please tick all that apply):	A patient with experience of the treatment being evaluated? (Kidney Transplant Patient, but not on Imlifidase) A patient organisation volunteer - Patient Representative
3. Name of your nominating organisation.	Kidney Care UK - Fiona Loud
4. Has your nominating organisation provided a submission? Please tick all options that apply.	No

5. How did you gather the information included in your statement? (please tick all that apply)	I am drawing from personal experience. I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). I have been a kidney patient since developing renal failure in 1977 and have experienced dialysis and transplantation. I have not completed part 2 of the statement as at this time I have no information on Imlifidase.

Living with the condition	
6. What is your experience of living with chronic kidney disease, and waiting for a transplant after being told you're considered highly sensitised and unlikely to receive a transplant as a result? If you are a carer (for someone with this condition) please share your experience of caring for them.	I was diagnosed with kidney failure at the age of 18 and within three months was on dialysis. As a "youngster I was fit and relatively well on HD. After a year and a half on HD I had my first transplant which lasted three months due to accurate rejection. During that time I was back and forwards to hospital, had treatments offered at that time including high dose steroids, (Pulse), heparin and plasmaphereasis. It wasn't the most pleasant experience for a 19 year old and when the doctor suggested a transplant nephrectomy and a return to Home HD it seemed to be like a return to some sort of normality. But, please remember I was young and fit and had done only a short time on dialysis at that stage and knew little about the long term effects of renal failure! After another 2 years on home dialysis I was offered a second transplant. Despite the outcome of the first transplant I jumped at the opportunity with absolutely no hesitation because I could see and feel that even after a short period on dialysis it was having an impact on my life and health. Despite a shaky start when I was told by the doctor they thought my second transplant would go the same way as the first, I have been exceeding lucky and the transplant I had in 1980 is still working well 41 years later. Since the transplant I worked full time for 35 years in reasonably senior roles for a local authority, got a degree with the Open University, took a year off and yacht raced round the world, have travelled widely around the world and enjoyed life throughly with NO restrictions. Since retiring I have sailed single handed round the UK. I live a "normal life". This would not have been possible on dialysis and I probably would not still be alive if I had not had a transplant!

7. What proportion of people with chronic kidney disease, who are highly sensitised and on the waiting list for a kidney transplant in England, need assistance from a carer?	Not known.

Current treatment of the condition in the NHS

8a. What do you think of the current treatments and care available for people who have chronic kidney disease and are waiting for a transplant (but are highly sensitised and considered unlikely to be receive a transplant) on the NHS? 8b. How do your views on these current treatments compare to those of other people that you may be aware of?	The main options for patients currently unable to have a transplant are haemodialysis or peritoneal dialysis or for some sadly it may be palliative care. Although dialysis keeps the patient alive it can be very restrictive in terms of being tied to home or a dialysis centre and live with fluid and dietary restrictions to keep the levels of toxins in the blood at reasonable levels. Dialysis involves “needling” a vein with two large needles to allow blood to flow through a kidney machine to purify the blood. This is a stressful and time consuming process which needs to be repeated two or typically three times a week taking up 5 hours or so each time. Peritoneal dialysis involves running bags of fluid into the abdomen allowing. Typically HD patients may have low Haemoglobin and have low levels of energy and after dialysis feel washed out. Due to the need for either regular HD or PD patients find It very difficult to travel, go on holiday, visit friends. Patients may also find trying to juggle treatments can cause difficulty with full time work. Regular treatments can cause relationship issues and mental health issues. Over the long term the prognosis for patients having some form of dialysis are typically poor and long term dialysis can cause many other medical complaints such as bone disease, heart disease etc. Long term patients may also have recurrent infections and also eventually run out of access to suitable blood vessels for HD. If I was a dialysis patient knowing I would never have a transplant and never get away from dialysis I would feel life was pretty pointless, particularly as I got older and probably had secondary heath issues. I think I would feel futile, angry and I am sure thoughts of suicide might even play on my mind. B) Many people cope (struggle on / exist) and others give up, while a few do well with good support mechanisms. Only a handful of patients I knew at the start of my journey back in the late 1970’s are still alive today! A transplant

	gives the opportunity for a longer, healthier and potentially more fulfilling life.

9. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how treatment is given or taken, side effects of treatment etc) please describe these	See section 8a also Dialysis, although it keeps patients alive has many disadvantages which can become more difficult to manage over time. Diet and fluid restriction, Tided to a hospital, treatment centre or home for daily or regular treatments. (Two or three times a week depending on treatment) Significant mental health issues Secondary health issues, like heart disease, bone disease and cancer. Social issues, treatment may preclude attending or interrupt meeting with family and friends and holidays may not be possible, more difficult to arrange or more expensive. Economic issues, unable to work, or unable to work full time due to treatment requirements or ill health. Time off for treatments and hospital appointments. **Other transplant anti rejection drugs. I have not been provided with any information on Imlifidase so I am unable to compare with existing treatments.** But existing treatments can cause many side effects, some short term and some due to long term use. For example long term use of prednisolone (steroid) can cause weight gain, diabetes, cataract, bone disease and heart disease. Long term use of drugs which suppress the immune system can lead to cancer and other complications. Even though like many other drugs, anti rejection drugs do have know side effects they are a risk that many patients feel it is worth balancing and taken for the freedom and independence from dialysis.

Advantages of this treatment

10a. If there are advantages of imlifidase over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 10b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 10c. Does imlifidase help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	**I have not been provided with specific advantages or disadvantages of imlifidase in terms of a treatment over current immunosuppressant drugs.** However, above I have described many of the issues associated with long term dialysis which in essence is the only treatment available for highly sensitised patients who are unable to have a transplant. Assuming this question is related to dialysis then I would say transplantation has many advantages. Obviously I am generalising as there are patients who do well on dialysis, but there is significant medical research to back up my anecdotal perspective that a successful transplant opens up a world of opportunities that are much more challenging and even impossible on dialysis. Quality of life - likely to have a longer, more productive and fulfilling life with a successful transplant. Health - Fewer health issues Social - More likely to sustain long term relationships and friendships as health is improved and many hours a week are not lost to having to have treatment. Economic - Transplant patients can return to full time work after a period of recovery after the operation, be a tax payer and make a contribution to society. Mental health - A transplant offers the potential for all of the above which can significantly reduce an individual's mental health issues and that of their family. 10b) Overall quality of life 10c) Yes, a successful kidney transplant offers a light at the end of the tunnel which is dialysis.

Disadvantages of this treatment	
11. If there are disadvantages of imlifidase over current treatments on the NHS please describe these. For example, are there any risks with imlifidase? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	**I have not been provided with any information on Imlifidase so I am unable to compare with existing treatments.** I am sure Imlifidase does have side effects, but as a transplant patient of many years, taking immunosupppresant drugs which also have side effects I am pretty sure once the side effects of Imlifidase had been explained to me I would more then likely take the opportunity that a successful transplant would offer over long term dialysis. We don't live in a risk free world and sometimes you have to balance these for the opportunity of a more fulfilling life.

Patient population	
12. Are there any groups of patients who might benefit more from imlifidase or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	**I have not been provided with any information on Imlifidase so I am unable to compare with existing treatments.** However, dialysis patients who have been unable to have a transplant due to being highly sensitive would benefit the most. At the present time they have little to look forward to other than a life of regular dialysis, typically 4 or five hours twice or three times a week plus travel to and from the dialysis centre and all the other health issues and life style restrictions listed above. A transplant offers them freedom from their “life sentence” and opportunity should they wish to grasp it. If I were to pick patient groups which were less likely to benefit I am not sure I would pick those listed. I suspect those with serious other health issues such as cancer due to possible recurrence, and heart disease that could be aggravated by the treatments given during a transplant. I could see many benefits to enabling dialysis patients with mobility, dexterity and cognitive impairments a transplant if it offered them a better quality of life.

Equality

13. Are there any potential equality issues that should be taken into account when considering this condition and imlifidase? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	**Yes. Kidney disease dose not effect everyone equally** People from lower socioeconomic groups are more likely to develop kidney disease, progress faster towards kidney failure and die. People from BAME communities are more likely to progress faster towards kidney failure and less likely to receive a kidney transplant. Women are more likely to be diagnosed with chronic kidney disease and men are more likely to start dialysis. There are more people with kidney disease in areas of social deprivation. Access to dialysis in rural areas can be very challenging. There are high rates of mental illness amongst people with chronic kidney disease and people on dialysis

real and https://www.gov.uk/discrimination-your-rights.	

Other issues	
14. Are there any other issues that you would like the committee to consider?	It is very hard to get across what living with chronic kidney disease is really like. Once you join the club you are a life member which exert Hugh mental as well as physical issues on the individual and their families. Even when you have had a successful transplant it is not a cure but it offers hope and opportunity! There is no escape so it is vital in my humble opinion that dialysis patients who are highly sensitised are also given an opportunity and hope for a better life.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the issues and questions below, but you do not have to comment on every issue or answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Issues in the ERG report	
Key issue 1: Relevance of comparators and methodological uncertainty	Please provide your response to this key issue, including any new evidence, data or analyses The ERG documentation seems to highlight a number of issues with the companies comparators and methodology which need to be clarified

Key issue 2: Placement of imlifidase in the UK treatment pathway	Please provide your response to this key issue, including any new evidence, data or analyses I am aware of patients who have been on dialysis for 20 years and not received a transplant due to being highly sensitised so if Imlifidase a safe alternative to the other very limited treatments currently available for sensitised patients I support it's introduction into the UK treatment pathway. For a sensitised patient who accepts a kidney from a relative or an altruistic donor the emotions pressures must be enormous and the desire and hope that the kidney will not be rejected are a Huge part of the decision to accept the organ and therefore if Imlifidase also makes kidney's from deceased donors available to this group this is also a major benefit.
Key issue 3: Generalisability of the evidence to NHS contexts	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 4: Interpretation of treatment outcomes following transplant	The ERG response appears to indicate that a number of key outcomes need to be clarified. For all kidney patients treatments are a balance of risk of the treatment against reward from a successful transplant. For every patient this is an individual decision based on many circumstances and facts offered to the patient. But I imagine for a highly sensitised patient who has been on HD/PD for a period of time the opportunity and potential rewards offered by a transplant may well become very appealing. However, for any patient making the decision to accept an organ and to accept Imlifidase as a treatment patients will need to know the facts surrounding the treatment, including possibility of delayed graft function due to potentially longer cold ischemic times, expected long term eGRF, the possibility of serious acute rejection, drug side effects such as infections and how these compare with other treatments, and of course likely graft survival rates and how many years it may realistically last.
Key issue 5: Comprehensive-ness of the clinical evidence base	Please provide your response to this key issue, including any new evidence, data or analyses Not qualified to answer,
Key issue 6: Comparators in the economic model	Please provide your response to this key issue, including any new evidence, data or analyses Not qualified to answer.

Key issue 7: Quality of life data used in the economic model	Please provide your response to this key issue, including any new evidence, data or analyses I find the quality of life indicator one of the most challenging areas to interpret and comprehend in a financial and economic sense. In my untypical example, my transplant has lasted 41 years, I worked full time for 35 of those years, was a higher rate tax payer. I have lived over 2/3 of my life with a functioning gift of life and only about 1/3 with my own native kidneys and approximately 3 years on dialysis. If I had been a highly sensitised patient without the option of a transplant I would probably be dead or have many complications, would not have worked and paid taxes, would not have made the same contributions to society or yacht raced around the world or travelled extensively. For many dialysis patients they would do anything to have a successful kidney transplant! I realise it is the role of NICE, but how do you measure good health in financial / economic terms?
General questions	

15a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating the condition? Are any missing? Do all patients receive treatment, or are some monitored only?	Some patients do not receive treatment for a variety of reasons and if they have end stage renal disease they typically do not live long as the kidney is a vital organ.
15b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition?	Renal failure is a difficult illness to describe to the public, friends and family and therefore its impact on life difficult to comprehend. It is life long, even after transplantation there is the necessity to take immuno-suppressent drugs which have known side effects such as rising blood pressure, increased risk of infection, heart disease and cancer. Life on dialysis can be immensely challenging as described earlier and generally the quality of life is much lower compared to the general public. Life expectancy is shortened.
15c. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured?	Identified earlier Improved quality of life - no longer just in survival mode, more able to fulfil Maslows hierarchy of needs Increased life expectancy Overall health bebefits over dialysis Freedom from dialysis and other restrictions such as diet and fluid Increased control over own destiny More opportunity and capacity to contribute to wider society

15d. What are the benefits of this treatment for carers?	

16. Are there any important issues that have been missed in ERG report?	Are there any implications of Imlididase treatment in the post covid-19 world for a transplant patient, for example on the likelihood of infection compared to other treatments and reducing the efficacy of the vaccine? If hepatitis C is going to be an exclusion as identified in one of the trials what percentage of the sensitised patient pool have positive Hepatitis C?

PART 3 – Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Imagine if you can the monotiny, weariness and exhaustion you would feel if you needed frequent (daily or multi days a week treatment lasting many hours) to allow you to survive year in year out for the rest of your life
- Add to this the restrictions of dialysis, the impact on family, friends, employment, visits, days out, holidays and the overall quality of your life. The inability to be spontaneous, to for example stay over with friends, go out on a sunny day!
- Add to this the mental anxiety this lack of control and personal freedom causes even the strongest person.
- A successful transplant gives the opportunity for a longer, healthier and potentially more fulfilling life with freedom to do what you want when without though or hesitation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please tick this box if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our **privacy notice**.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **11 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating people with chronic kidney disease who are highly sensitised and awaiting a transplant from a deceased donor, and current treatment options	
About you	
1. Your name	**Colin Geddes**
2. Name of organisation	**Glasgow Renal and Transplant Unit, UK Renal Association**
3. Job title or position	**Consultant Nephrologist and Honorary Clinical Associate Professor**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with kidney transplant rejection in people with chronic kidney disease? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Relevance of comparators and methodological uncertainty	In several places it is stated that it would be unethical to perform a randomised controlled trial because there is no approved comparator. I disagree. I believe it would be ethical to conduct a randomised controlled trial where the control group receives standard care of waiting for a suitable transplant from the national Kidney allocation scheme. This would enable a meaningful comparison of patient survival, quality of life, adverse events and cost.
Key issue 2: Placement of imlifidase in the UK treatment pathway	
Key issue 3: Generalisability of the evidence to NHS contexts	The kidney allocation scheme in UK is specific to UK so makes comparisons difficult. Also the living donor national kidney sharing scheme in the UK is very successful and offers highly sensitised patients a good alternative to deceased donation if they have a suitable living donor.

Key issue 4: Interpretation of treatment outcomes following transplant	The available data are still too focussed on the short term. Our understanding of donor specific HLA antibodies is that, if they are present post transplant either because they were pre-formed or because they have formed de-novo, then they tend to cause long-term damage for which there is no known effective treatment and which tends to shorten the life of the transplant considerably. Therefore 6 month or even 2 year graft survival is still a short outcome measure for a treatment that is known to be associated with return of donor specific antibody.
Key issue 5: Comprehensiveness of the clinical evidence base	The fact the evidence base consists of phase 2 uncontrolled trials of small numbers of subjects with relatively short follow up is a significant limitaiton
Key issue 6: Comparators in the economic model	The economic model makes assumptions about the long-term survival of the kidney transplant that are not supported by long-term data yet
Key issue 7: Quality of life data used in the economic model	Please provide your response to this key issue, including any new evidence, data or analyses
Are there any important issues that have been missed in ERG report?	Changes in the UK deceased donor Kidney Allocation scheme would be required to incorporate Imlifidase in to the treatment pathway. All of the issues above have been addressed by the ERG report.

PART 3 – Key messages
16. In up to 5 sentences, please summarise the key messages of your statement: • • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Clinical expert statement & technical engagement response form

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **11 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating people with chronic kidney disease who are highly sensitised and awaiting a transplant from a deceased donor, and current treatment options	
About you	
1. Your name	**Dr Sunil Kumar Daga**
2. Name of organisation	**Leeds Teaching Hospitals NHS Trust**
3. Job title or position	**Consultant Nephrologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with kidney transplant rejection in people with chronic kidney disease? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment and avoiding kidney transplant rejection in people with chronic kidney disease who are highly sensitised and 'unlikely to be transplanted'	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of proposed treatment is to allow a window for transplantation in people with chronic kidney disease who are highly sensitised and 'unlikely to be transplanted' by reducing antibodies using the proposed drug (but alongside of a developed protocol to manage when antibodies rise again and risks rejection).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Rejection free and transplant graft and patient survival at 3 months, one, three and five years

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	In my views, the unmet need is for specific proportion of cases with 100% cRF as the 2019 national kidney allocation scheme has been developed to reduce inequalities of highly sensitised patients (HSP) and the benefit is more for cases with cRF 85-99%. Data from 5-months confirmed the benefit with 246 HSP received transplant (https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17898/bts-2020-early-impact-of-the-2019-kos-5-month-results.pptx).
What is the expected place of the technology in current practice?	
11. What is currently done in the NHS for people with chronic kidney disease who are highly sensitised and unlikely to be transplanted? For a specific question on people who are 'unlikely to be transplanted', please see question 24. For a specific question on types of dialysis, please see question 26. For a specific question on transplantation in this group,	Number of interventions are currently been done in NHS for people with chronic kidney disease who are highly sensitised and unlikely to be transplanted 1. If they have a living kidney donor - National Living Donor Kidney Sharing Scheme (NLDKSS) has about 39% HSP and so far 26% of 1029 transplants were in HSP. The 5 year outcome of paired exchange living donor transplant scheme is 92.1 % (95% CI = 87-95) as compared to HLA incompatible which is 81.4% (95% CI= 75-86). (ref - https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17922/bts-2020-sharing-living-kidneys-what-difference-does-it-make.pptx) 2. As a result of above direct HLA-incompatible transplantation is rarely performed in UK; but remains an option if no offer after 4 runs in NLDKSS 3. When there is no option of living donor, centres are using delisting strategies - removing unacceptable HLA antigen with antibody response of mild and moderate intensity with a view to have cross match negative transplant with augmented immunosuppressive medication regimens. Similarly, centres can delist HLA antigens which are perceived high immunological risk but has no antibody responses (either with historic positive or repeat mismatch) but accounts for cRF and thus define some cases as highly sensitised. This is undertaken based on local protocols and differs across the country. 4. 2019 National allocation scheme is promising with increase transplantation for HSP (https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17898/bts-2020-early-impact-of-the-2019-kos-5-month-

please see question 27.	results.pptx). 5. Part of clinical trials - such as on-going trial of desensitisation on waiting list in the UK (ref - http://www.isrctn.com/ISRCTN66441193).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	1. Guidelines for Antibody Incompatible Transplantation http://bts.org.uk/wp-content/uploads/2016/09/06_BTS_Antibodies_Jan2011.pdf 2. The detection & characterisation of clinically relevant antibodies in allotransplantation https://bts.org.uk/wp-content/uploads/2016/09/06_BTS_BSHI_Antibodies-1.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined as per the allocation scheme but how clinically relevant antibodies are defined varies across the centres such that same case sometimes may have a large difference in cRF if assessed at two different transplant centres. This is partly because different laboratories draw different threshold values of the assay used (Luminex Screening or Single antigen bead assay) for example one centre may have 500 as cut-off for positivity whereas other may have 2000!.Similalr threshold definition varies in delisting strategies too where centres would be happy to remove unacceptable definition by ignoring a moderate level of MFIs. Also, it is important to bear in mind that cRF is also determined by other unacceptable HLA antigens defined by individual teams even when they are negative for antibodies based on above threshold such as mismatched Antigens on previous failed transplants to which specific antibody has not been demonstrated, or a historic positive but currently negative for years. The reason for discrepancy is based on caution some centres would take to avoid a possible memory responses. Hence, how an unacceptable antigen is defined varies and that has effect on overall cRF and thus HSP status of a patient.
• What impact would the technology have on the current pathway of care? For a specific question relating to the Kidney	It is not clear to me currently as the 2019 scheme has only reported data on 5-month results and has shown promising results with increased compatible transplantation using standard immunosuppressive medications in HSP (https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17898/bts-2020-early-impact-of-the-2019-kos-5-month-results.pptx).

Offering Scheme, please see question 25.	Also, the technology is for patients with presence of HLA-specific antibodies and some of the cRF contributions is from other considerations such as avoiding repeat mismatches and avoiding memory responses if historic antibodies were present. I am concerned that the technology will require change to current pathway of care which is currently based on compatible kidney transplantation with no HLA antibodies response post transplantation and the risk of antibody mediated rejection been minimal (2.5 to 5% in standard risk); whereas the proposed technology only allows a window of a week with no antibodies and the pathway of care will require monitoring of rise of antibodies with modification / augmentation of immunosuppressive drugs and treatment of accompanied rejection (which is reported as 30-50%). Both monitoring of antibodies and augmentation of immunosuppressive treatments are significant deviation from current pathways. It is very likely these cases will require longer length of hospital stay too.
12. What would be the appropriate positioning of imlifidase in the NHS?	I am not sure for wider use for all cases defined as HSP and would suggest this should be reserved for few select cases such as 100% cRF despite delisting low to moderate level HLA-specific antibodies or cases on dialysis with poor dialysis access such that without transplantation, their life will be at risk. Due to special monitoring requirement and management of augmented immunosuppression and higher risk of rejection, the Imlifidase should only be used by specific centres with expertise and resources to safely manage these cases and complications.
• How would healthcare resource use differ between the technology and current care?	Yes a significant resources will be required - H&I and histopathology lab turn over ideally on weekend too. Availability of plasma exchange and biologics such as ecluzimab or rituximab; and facility for splenectomy for extreme case of rejections.
• In what clinical setting should the technology be used? (For example, specialist renal centres)	Only specialist centres who has experience in managing antibody incompatible transplantation/ delisting strategies and have all MDT resources to manage these cases safely (until enough national experience is achieved and good practises are shared/ learnt)
• What investment is	Human resource investment will be required to timely report antibody and histology results, to safely administer

needed to introduce the technology? (For example, for facilities, equipment, or training.)	complex biologic drugs and plasma exchange.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I am not sure as enough data both in scale and follow-up are not there and absence of controlled trial makes it very hard to expect clinically meaningful benefits.
• Do you expect the technology to increase length of life more than current care?	I am not sure as depending on progress following transplant with augmented immunosuppressant and rejections, this may on the contrary increase risk of shorter life and poor quality of life with significant morbidities
• Do you expect the technology to increase health-related quality of life more than current care?	As above
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the full indication population?	The technology is likely to less effective in cases that would be transplanted against multiple mismatch against which they had antibodies prior to treatment and likely to rebound after a week and cause severe acute antibody mediated rejection.
The use of the technology	

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There will be a learning curve but it is likely to remain challenging for both patients and healthcare professionals, partly due to lack of larger and longer term data to make the informed decision and partly due to careful selection of the cases for this treatment. A change in induction protocol will be required as the Imliflidase cleaves IgG such as basiliximab, alemtuzumab, rabbit anti-thymocyte globulin and IVIg. Most centres in UK would use these at time of perfusion (transplant surgery) to prevent activation of navie lymphocyte and thus adaptive immunity by allorecognition but also against memory lymphocyte to prevent aggressive immune response to transplant graft and thus rejection. Although not tested in the phase 1/2 trials (as reported), it might be possible to prepare case using these agents few days prior to Imlifidase and semi-elective deceased donor transplantation. Ideally a Deceased Brain Death (DBD)transplant be preferred compared to Deceased Cardiac Donor (DCD) to avoid Delayed Graft Function (DGF). DSA monitoring will be required following transplantation, although the studies mention no rebound until after a week, there will be variability and transplant across higher cumulative DSA MFI prior to Imlifidase will require earlier day 3-5 or sooner if lack of primary function. The centres should have access to DSA testing and histology all seven days ideally and initially only centres who are currently familiar with desensitisation regimen and manages antibody incompatible transplantation should use Imlifidase with wider use perhaps after a period of national data analysis.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As above

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes the technology is innovative and hopefully will make substantial impact. It would have been useful to conduct a randomised controlled trial comparing the technology with current approaches in light of new allocation scheme; hence it would be important to maintain a register of cases who may receive this drug and report outcome regularly.
• Is the technology a 'step-change' in the management of the condition?	It will be a step change and open option for managing cases where current approaches has not worked
• Does the use of the technology address any particular unmet need of the patient population?	Yes, Tier 1 wait listed patients particularly who has not received offer despite one year of introduction of the scheme
19. How do any side effects or adverse effects of the technology	As the technology is non-specific and cleaves all IgG of patient, risk of infection/ sepsis need to managed well as they can be associated with poor quality of life. Also the rebound of antibodies and associated rejection is going to

affect the management of the condition and the patient's quality of life?	add to morbidity. These needs to be counselled and balanced against risk of not transplanting and staying on dialysis/ waiting list.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	No, in UK clinical practice are based on higher level of clinical trial - Randomised Clinical Trial using the proposed novel treatment against standard of care unless select case have prospectively introduced desensitisation protocols.
• If not, how could the results be extrapolated to the UK setting?	The studies has not included any patients/ centres in UK setting, but there are common parallel from baseline - particularly 25 cases summary (Table 17)
• What, in your view, are the most important outcomes, and were they measured in the trials?	The following are important measures in the trials - conversion to negative Cross match at time of transplant, rebound of DSA and timing, AMR incidence, infections and mortality and short term outcomes. The measures that would be useful but not reported are incidence of isolated cellular rejection (particularly vascular rejection) as induction therapy may be infective due to cleavage by Imlifidase, AMR at one year and longer term outcome such as 3 and 5 year graft and patient survival.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcome measures such as baseline cross match - particularly CDC positive cross match, multiple DSAs were associated with 5-year outcome of Antibody incompatible kidney transplantation in UK (The UK national registry of ABO and HLA antibody incompatible renal transplantation: Pre-transplant factors associated with outcome in 879 transplants. Transplant Direct 2017; 3(7): e181. Late AMR (> 6/12 following transplantation) is a useful surrogate

	marker of long term clinical outcomes and follow-up studies may help establish this in context of Imlifidase.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Trial data (Table 17) do compare to real-world experience in lot of ways but detail is missing on specificities of immunodominant HLA as for example transplantation in case with high HLA-Cw DSA in 12000 with some B-cell reactivity in absence of any other high level DSA can be undertaken with modification of baseline IS medications. Also small number (N= 25) may risk not representing the wider heterogeneity of clinical decision for individual patient context.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No, there are no equality issues when considering this treatment as such but application of the technology and individual centre practises may create equality issue when implementing this as evidence by wide difference in waiting times across centres in UK.

23b. Consider whether these issues are different from issues with current care and why.	No, these issues are likely to amplify with current practise with different risk aversion /behaviour of individual centres
23c. What are the differences in mortality, quality of life and other effects if a patient undergoes standard non-sensitised transplantation compared to the wait time or lack of access of a very highly sensitised patient?	UK data suggest increase in mortality of highly sensitised patients with 10% mortality in 5-year waiting with also further increase in morbidities resulting in removal from waiting list (15%); thus these patients generally would be experiencing poor quality of life while waiting for standard non-sensitised transplantation.
Topic-specific questions	
24. Which people would be in the 'unlikely to be transplanted' group? How do clinicians decide that someone is 'unlikely to be transplanted', or what would make them think someone was in that group? Would any specific criteria/parameters or a combination of criteria/parameters be used in practice (and at what	'Unlikely to be transplanted' group depends on number of factors and clinicians alone don't decide on these factors that makes someone in this category. The key aspect to this is how we define an unacceptable antigen in UK and this is heterogeneity in practise across centres - with different threshold to define positive on Single Antigen Bead assay (500-2000 for standard risk and 2000-5000 for delisting strategies), variation in practise in defining unacceptable where there is no reactivity (antibodies) against the HLA (repeat mismatch, split antigen and historic positive).These policies are defined by clinical scientists in transplant immunology lab in collaboration with clinicians at some centres. Also, some centres would like to avoid higher immunosuppressant burden and avoid 2DR mismatch kidney and list that as unacceptable and thus contribute to waiting time. 100% cRF remains a challenge despite new allocation scheme - early data suggested small increase compared to

level)? How does this translate into a likely number of people eligible for treatment with imlifidase in the NHS? Which patients would you want to use this treatment for, it it were to be approved for use in the NHS – what distinguishes them from other people who are highly sensitised that you treat for renal replacement therapy?	2006 scheme (4% versus 2%) with greater benefit for other category of HSP (cRF 85-99%) 19% versus 11%. Similarly, waiting over 7 years had no impact (ref - https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17898/bts-2020-early-impact-of-the-2019-kos-5-month-results.pptx). Hence a particular group of people who could be considered unlikely for transplanted in current kidney allocation scheme would be those waiting over 7 years and cRF of 100% (despite delisting criteria applied). I would offer this treatment to such cases and others I would like to wait for at least one year wait on current Tier 1 unless clinically desperate situation (like failing access)
25. What impact could this technology have with respect to the Kidney Offering Scheme? How could it affect other groups of people waiting for a kidney transplant from a deceased donor? Would any changes to the algorithm potentially need to be made?	It depends on the cases this technology is used, if offered to patients waiting over seven years - then no change is required. However, if certain cases falls under Tier 1 and would be moved to Tier 2 as a result of the treatment (due to delisting large number and thus driving cRF down) then we would need to do a change in allocation scheme with retaining previous (pre-treatment) cRF for such cases. In such cases there would be lot more transplants happening in Tier 1 and after certain time we may need to revisit the criteria and lower the waiting time to 5-year (ascompared to 7 year).
26. In clinical practice, do all	I am not familiar of exact statistics but based on waiting time of over seven years and cRF of 100% (‘unlikely to be

people who are highly sensitised and awaiting a kidney transplant but considered 'unlikely to be transplanted' receive dialysis? Of the patients that receive dialysis, what proportion receive haemodialysis, and what proportion receive peritoneal dialysis?	transplanted') - all of these are likely to be on dialysis with majority on hemodialysis. However, a significant proportion of highly sensitised patient may be either pre-emptive with some native kidney function or failing transplant.
27. In the NHS in England, how many people with chronic kidney disease awaiting a transplant from a deceased donor, who are considered 'unlikely to be transplanted', actually receive a transplant? Is this purely through a match becoming available, or are desensitisation techniques (not including imlifidase) used to facilitate this? What are outcomes like for these people after transplant, especially in terms of	Early data suggested small increase in transplantation in cases with cRF of 100% compared to 2006 scheme (4% versus 2%) with greater benefit for other category of HSP (cRF 85-99%) 19% versus 11%. Similarly, waiting over 7 years had no impact (ref - https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17898/bts-2020-early-impact-of-the-2019-kos-5-month-results.pptx). This is due to change in allocation scheme which is only a year old (2019) and further data will be available in February 2021 BTS conference. Some of these transplant happens due to delisting strategies too and their outcome are good (however no data collected nationally on these cases) but likely to vary depending on delisting criteria employed.

graft failure and graft rejection (both short term and long term), and length of time to next kidney transplant, compared to people who are not considered 'unlikely to be transplanted'?	
28. What is the average wait time in tier 1 for patients who are highly sensitised but considered likely to receive a transplant? For patients who are unlikely to receive a transplant in the tier 1 priority programme, what proportion are waiting more than a) 5 years b) 7 years? What proportion are eventually taken off the waiting list?	Overall 5% of active patients are waiting more than 7 years (and 9 % > 5 years) as per 2020 report (https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/20032/kidney-annual-report-2019-20-final.pdf). I am not able to find exact data for this and it may be useful to write to NHSBT Statistics (statistical.enquiries@nhsbt.nhs.uk)
29. What proportion of people with chronic kidney disease, who are highly sensitised and on the waiting list for a kidney transplant	I am afraid, I don't know the answer to this question

in England, need assistance from a carer?	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Relevance of comparators and methodological uncertainty	Please provide your response to this key issue, including any new evidence, data or analyses I feel one of the other comparator and even a small pilot study in UK would be useful a) Imlifidase versus maximal delisting strategies in context of 2019 kidney allocation scheme
Key issue 2: Placement of imlifidase in the UK treatment pathway	Please provide your response to this key issue, including any new evidence, data or analyses This will require further work with clinical consensus on 1. Uniform way to define unacceptable antigen (thus cRF) and maximal delisting strategies 2. Defining immunosuppressive pathways with testing semi-elective deceased donor transplantation and preparing of patients - particularly long waiter (>7 year) 3. Defining optimal monitoring and pre-emptive biopsy for very high risk cases where DSA rebound can be in day 3-5 post transplantation 4. Identification and clinical use in limited transplant centre with experience of managing HLA-incompatible kidney transplantation (before wider adoption)

Key issue 3: Generalisability of the evidence to NHS contexts	Please provide your response to this key issue, including any new evidence, data or analyses As above in key issue 2
Key issue 4: Interpretation of treatment outcomes following transplant	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: Comprehensiveness of the clinical evidence base	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 6: Comparators in the economic model	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 7: Quality of life data used in the economic model	Please provide your response to this key issue, including any new evidence, data or analyses
Are there any important issues that have been missed in ERG report?	

PART 3 – Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Practise of defining unacceptable antigen (thus cRF) by laboratory and clinical team are varied and when this technology is made available it would be important to have UK national standards agreed
- Patients 'unlikely to be transplanted' in the new 2019 kidney allocation scheme requires further clarification - data on one year of the scheme should be ready by February 2021
- As the Imliflidase only prevent hyperacute rejection and provide a window for transplantation, careful monitoring for acute rejection and optimisation of immunosuppressive protocol with access to transplant immunology and pathology required, thus initially this should be allowed in few transplant centres with expertise of HLA-incompatible kidney transplantation before wider rollout after review of practise and outcomes
- Data from phase 1/2 studies are very small in context of this scope (n=25) and thus a national registry of outcome and review should be established to capture both immediate and long term data
- If successful this technology will transform opportunities of transplantation to very highly sensitised patients that would be hard to achieve with current practises.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **11 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating people with chronic kidney disease who are highly sensitised and awaiting a transplant from a deceased donor, and current treatment options	
About you	
1. Your name	**Nicholas TORPEY**
2. Name of organisation	**British Transplantation Society**
3. Job title or position	**Consultant Nephrologist, Addenbrooke's Hospital, Cambridge** **And** **Treasurer, British Transplantation Society (BTS)**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with kidney transplant rejection in people with chronic kidney disease? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**
The aim of treatment and avoiding kidney transplant rejection in people with chronic kidney disease who are highly sensitised and 'unlikely to be transplanted'	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Facilitate a successful transplant, as opposed to many years on the transplant waiting list with little prospect of being offered a kidney

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Offer of a kidney through the 2019 Kidney Allocation Scheme
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Absolutely. At least 80% of the cRF 100% cohort of waitlisted patients (537 patients out of a total active waiting list of 4938 as of Feb 2020) would not be transplanted under the 2006 Kidney Allocation Scheme. At the very best, the revised 2019 scheme may allow transplantation of 40% of these patients (I suspect fewer), so there remains a very substantial unmet need.
What is the expected place of the technology in current practice?	
11. What is currently done in the NHS for people with chronic kidney disease who are highly sensitised and unlikely to be transplanted? For a specific question on people who are 'unlikely to be transplanted', please see question 24. For a specific	1. Wait-listing on the deceased donor waiting list 2. Participation in the UK living donor kidney sharing scheme (UKLKSS) for those with an incompatible live donor 3. Very careful management of wait-list restrictions and targeted allocation of compatible / acceptable kidneys to these patients 4. With these approaches no more than 40% of this group would reasonably be expected to receive a transplant, often after many years of waiting (see points below and slide presentation provided separately)

question on types of dialysis, please see question 26. For a specific question on transplantation in this group, please see question 27.	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No specific national guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The approach to highly sensitized patients (cRF >99%) varies considerably between transplant units, but the outcome (very low transplant rates) is broadly similar. The availability of an intervention that allows transplantation of these patients will allow for the development of a defined national protocol (patient selection and management), optimizing patient outcomes
• What impact would the technology have on the current pathway of care? For a specific question relating to the Kidney Offering Scheme, please see question 25.	It would be straightforward to modify patients wait-listing, although a clear national policy (in cooperation with NHSBT) would be necessary

12. What would be the appropriate positioning of imlifidase in the NHS?	
• How would healthcare resource use differ between the technology and current care?	Current care in effect commits these patients to a lifetime of dialysis. Allowing access to transplantation frees these patients from costly dialysis (and associated complications)
• In what clinical setting should the technology be used? (For example, specialist renal centres)	Transplant centres with expertise in managing high-immunologic risk patients. In my view Imlifidase use should be restricted to a few centres willing to accept referrals from a wide region – maybe 4 out of 19 adult transplant
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The necessary infra-structure already exists (clinical programs and HLA labs with the ability to perform pre-transplant cross-match testing and HLA antibody screening).
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes – survival following a successful transplant is better than that should patients remain on dialysis. The precise benefit for an individual patient is hard to predict.

• Do you expect the technology to increase health-related quality of life more than current care?	Definitely – many studies have demonstrated improved QoL with transplantation as opposed to dialysis
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the full indication population?	If the intervention is focussed on cRF 99-100% patients then this represents a homogenous group
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There will be specific requirements for those transplant centres utilizing Imlifidase – especially the need for rapid turnaround cross match testing and HLA antibody screening – although both of these are already available. Follow-up monitoring of HLA antibody levels and kidney biopsy is already standard of care. The immunosuppression required, in addition to Imlifidase, includes T-cell depletion, IVIG and rituximab. None of these are routinely commissioned for transplantation, and this point will need to be addressed.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	In my view Imlifidase should be introduced as part of a structured national program including NHSE and NHSBT
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes – there has never been an intervention that allows for rapid cross match conversion / DSA removal in a timeframe compatible with deceased donor kidney transplantation

• Does the use of the technology address any particular unmet need of the patient population?	Unquestionably – see (10) above and the discussion in Part 3 below
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Few, if any, adverse effects beyond that of post-transplant immunosuppression
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials are innovative and offer a unique solution to the clinical problem. In that sense the trials are a step-change in clinical practice, not a reflection of it.
• If not, how could the results be extrapolated to the UK setting?	Published results of Imlifidase can be applied to highly sensitized patients in any country
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes they were – AMR, graft survival and patient survival – although all relatively short term (1 year)
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The main concern is of long-term outcomes – how long will the kidney last – and the potential to develop chronic antibody-mediated rejection.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Insufficient data as yet
22. How do data on real-world experience compare with the trial data?	The only experience is that reported in trials
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Imlifidase promotes equality by making kidney transplantation a possibility for a group of patients otherwise very unlikely to be transplanted.

23b. Consider whether these issues are different from issues with current care and why.	
23c. What are the differences in mortality, quality of life and other effects if a patient undergoes standard non-sensitised transplantation compared to the wait time or lack of access of a very highly sensitised patient?	Please see 'Outcomes' in Part 3 below
Topic-specific questions	
24. Which people would be in the 'unlikely to be transplanted' group? How do clinicians decide that someone is 'unlikely to be transplanted', or what would make them think someone was in that group? Would any specific criteria/parameters or a combination of criteria/parameters be used in practice (and at what	In my view the unlikely to be transplanted group are straightforward to define – those with a cRF of 99 – 100% and an HLA antibody profile that does not allow the offering of a compatible or low risk incompatible kidney. The numbers are described in (10) and Part 3 below.

level)? How does this translate into a likely number of people eligible for treatment with imlifidase in the NHS? Which patients would you want to use this treatment for, it it were to be approved for use in the NHS – what distinguishes them from other people who are highly sensitised that you treat for renal replacement therapy?	
25. What impact could this technology have with respect to the Kidney Offering Scheme? How could it affect other groups of people waiting for a kidney transplant from a deceased donor? Would any changes to the algorithm potentially need to be made?	The purpose of the 2019 Kidney Offering Scheme was to promote equity of access to transplantation. The initial experience of the 2019 scheme suggests that patients with a cRF up to 99% can be transplanted with a waiting time equivalent to non-sensitized patients, but those with cRF >99% wait much longer, and may never be transplanted (see above). Accordingly use of Imlifidase promotes equity of access for this very challenging group of patients. Changes to the allocation algorithm would not be needed – what would change is the patients' listing and definition of unacceptable HLA specificities. A protocol to allow Imlifidase use would need to be agreed with NHSBT.

26. In clinical practice, do all people who are highly sensitised and awaiting a kidney transplant but considered 'unlikely to be transplanted' receive dialysis? Of the patients that receive dialysis, what proportion receive haemodialysis, and what proportion receive peritoneal dialysis?	Yes. Patients can be listed for a transplant when they are within 6 months of dialysis. Since the median waiting time to transplant for cRF 100% patients is 7 years, the vast majority will be dialysis dependent – and that is just those that are transplanted. The remaining 80% (under the 2006 scheme) are inevitably dialysis dependent.
27. In the NHS in England, how many people with chronic kidney disease awaiting a transplant from a deceased donor, who are considered 'unlikely to be transplanted', actually receive a transplant? Is this purely through a match becoming available, or are desensitisation techniques (not including imlifidase) used to facilitate this? What are outcomes like for these people after	I have addressed this point in Part 3 in detail, and I the separate slide presentation

transplant, especially in terms of graft failure and graft rejection (both short term and long term), and length of time to next kidney transplant, compared to people who are not considered 'unlikely to be transplanted'?	
28. What is the average wait time in tier 1 for patients who are highly sensitised but considered likely to receive a transplant? For patients who are unlikely to receive a transplant in the tier 1 priority programme, what proportion are waiting more than a) 5 years b) 7 years? What proportion are eventually taken off the waiting list?	We do not know because the 2019 Kidney Offering Scheme was only implemented in September 2019, and then disrupted during the COVID pandemic. However, 11% of the cRF 100% patients were transplanted in the first year (and so 89% still waiting). Under the 2006 scheme median waiting time was >7 years, but this of course only applies to those transplanted. The majority were not transplanted
29. What proportion of people with chronic kidney disease, who are highly sensitised and on the	I do not know!

waiting list for a kidney transplant in England, need assistance from a carer?	

PART 2 – Technical engagement questions for clinical experts – I completed the BTS response to technical engagement

PART 3 – Key messages

Highly Sensitized

1. The problem here is that there is no accepted definition of highly sensitized. In the UK, until September 2019, there was an arbitrary definition of highly sensitized as a cRF of 85% or more (cRF is a measure of how many potential donors an individual recipient 'reacts' against – as measured by HLA antibody screening - and so cannot receive a kidney from that proportion of donors). This definition was embedded in the 2006 Kidney Allocation Scheme.

2. However in September 2019 the kidney allocation scheme was radically overhauled, and highly sensitized in effect became a cRF of 100% (more accurately >99%) – these patients comprise Tier A of the 2019 Kidney Allocation Scheme (KAS)

3. There is quite good evidence that focussed kidney allocation algorithms can allocate compatible (or at least acceptable) kidneys equitably to wait-listed recipients with HLA sensitization up to 99% - so these patients wait no longer than non-sensitized patients. Although disrupted by COVID, the first year of the UK 2019 KAS is consistent with this claim.

4. So, in contrast to the Hansa submission and PenTAG analysis I would say that highly sensitized is a cRF of >99%.

5. In my view this creates a far more focussed group of patients than that presented to NICE by either party. It also defines a group of patients who are very unlikely to receive a kidney transplant and massively simplifies the financial analyses. Here are the pertinent facts:

    a. cRF 100% patients comprise 10.9% of the entire deceased donor waiting list (537 of 4938 patients listed as of February 2020 – COVID prevents reliable data after that point) – in fact cRF 100% is the second largest group of patients in the waiting list – the largest being cRF of 0% (about half the waiting list).
    b. Under the 2006 KAS only 2% of transplants / year were in this group, and those that were transplanted had a median waiting time from listing to transplant of 7 years.
    c. Under the 2006 KAS about 80% of these patients would not be transplanted – most either died whilst waiting or were removed from the waiting list having become unfit.

d. A very informative patient cohort is those with a cRF of 100% who have an incompatible living donor, and so are enrolled in the living donor sharing scheme. Between June 2007 and Feb 2020 there were 238 cRF 100% patients enrolled in the kidney sharing scheme (out of a total of 2480). Those patients were also active on the deceased donor waiting list and over the entire 13 year period only 46 out of 238 (19%) received a deceased donor kidney – consistent with points (b) and (c) above.

6. The landscape has changed a little under the 2019 KAS. In the first year (Sept 2019 – Sept 2020) the proportion of transplants to CRF 100% patients increased from 2% to 4%, with 63 of the 537 receiving a transplant. Some caution is needed here because there will be a proportion of the cRF 100% patients who are relatively 'easy' to transplant – for example if their HLA type includes a common haplotype such as A1 B8 DR17 (I can elaborate further if needed!) Never the less the 2019 KAS will lead to more transplants in this cRF 100% group. It is too early to say exactly how many more – especially with COVID disruption – but a very similar approach in the US (effective since 2014) led to 20% of cRF 100% patients receiving a transplant over 3 years. I think the most optimistic interpretation is that the number of cRF 100% patients transplanted under the 2019 scheme is very unlikely to exceed 40% - leaving at least 60% un-transplanted. These are the obvious target for a strategy utilizing Imlifidase.

Outcomes

7. This is more difficult. For highly sensitized patients *receiving a compatible or acceptable kidney* in the US the outcomes for cRF 98-100% patients transplanted under the revised 2014 allocation scheme – in terms of graft and patient survival – are no different to non-sensitized patients (3 year patient survival and death-censored graft survival were excellent at 96%). The incidence of AMR was 13.6%, which is significantly above baseline (2-3% I the UK) (Jackson *et al* (2020). *Am J Transplant* **20**, 2890-98). In the Eurotransplant Acceptable Mismatch scheme – a targeted allocation system for very highly sensitized patients – the incidence of rejection was comparable to non-sensitized patients (Heidt *et al* (2019). *Am J Transplant* **19**, 2296-33)

8. In the UK the issue is more complicated. If a CRF 100% patient is allocated a *compatible* kidney then I suspect the outcomes are close to non-sensitized patients (that would be our experience in Cambridge). However, in an attempt to transplant these patients, many units would allow the allocation of an *incompatible* kidney. Incompatible in these circumstances would mean, for example, low level pre-formed donor-reactive HLA antibodies. The incidence of AMR (baseline 2% in non-sensitized patients) is probably increased to 10% for these low risk incompatible transplants but the long-term outcomes are reasonable. This is to some extent captured in our UK registry report, published in 2017 (Pankhurst *et al*, Transplantation Direct **3(7)**, page 181).

9. So for those highly sensitized patients, including those with a CRF of >99%) *who can be allocated a compatible or acceptable kidney* through careful wait-list management and allocation policy, the outcomes are likely comparable to non-sensitized patients. This is, of course, good news for those patients who can be transplanted.

10. However, I am not sure that this is especially helpful or relevant. The issue with the 'un-transplantable' 60% (or more) of the cRF 99-100% patients is that they will never be offered a kidney and that Imlifidase as part of a protocol that also includes T-cell depletion, IVIG and rituximab, does offer the possibility of a transplant. The most recent Hansa data suggests an AMR rate of about 33% in the first year, in most cases reversed by antibody-removal (plasma exchange or similar), and excellent 1 year graft survival (90%). These limited data to date suggest better outcomes using Imlifidase-based protocols than the UK historic experience – mainly using plasma exchange and in living donor kidney transplantation – where 1 year transplant survival for CDC cross match positive patients was just 72% (Pankhurst *et al* (2017), Transplantation Direct **3(7)**, page 181). What remains uncertain is long-term outcomes and in particular the development of chronic antibody-mediated rejection.

Summary

11. My own view (for what it is worth!) is that Imlifidase is the only potential intervention that will allow transplantation in this very disadvantaged group of patients for whom there is no alternative route to transplantation and as such are committed to a lifetime of dialysis. I am in favour of its use, but almost certainly as part of a nationally commissioned and regulated program with robust patient selection and data collection. I think concern over long-term outcomes is justified – although I also think the majority of this patient group would accept uncertainty over 5 and 10 year outcomes in return for 5 or 10 (or more) years off dialysis.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Monday 11 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Transplantation Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Relevance of comparators and methodological uncertainty	**NO**	Imlifidase treatment is aimed those highly sensitized patients very unlikely to receive the offer of a compatible kidney through the national Kidney Allocation Scheme (referred to as KOS in the ERG discussion). The reasonable comparison group is that same group of patients either (a) not transplanted, or (b) transplanted with a compatible kidney, which may necessarily impose many years of waiting. The ERG point to several uncertainties, and we would make the following points: 1. Although highly sensitized patients may well not have started dialysis at the time of listing, the overwhelming majority will become dialysis dependent whilst waiting for a compatible kidney. 2. The ERG raise the issue that by transplanting a patient using Imlifidase then another patient would not be transplanted. But this is necessarily the case for every deceased donor or living donor kidney transplanted. To speculate as to the impact on the whole waiting list is, we would suggest, almost impossible. Indeed, the majority of patients on the kidney waiting list are pre-dialysis and non-sensitized and so very likely to be transplanted with a different kidney in a short time with negligible additional cost. 3. Whilst there is some uncertainty over long-term outcomes, the concern over increasing cold ischaemic time (CIT) is probably unreasonable (see Key Issue 2 below).

Key issue 2: Placement of imlifidase in the UK treatment pathway	**NO**	We would anticipate a treatment pathway as follows: 1. Identification of appropriate wait-listed patients – for example cRF >95% or cRF 99% or more. 2. Identify those HLA specificities to which the patient has antibodies likely removed by Imlifidase – there is much discussion in the document as to how these specificities would be identified. In the UK wait-listed patients are extensively screened for HLA antibodies by solid phase assay (typically Luminex) that allows prediction of cross match results (flow cytometry or cytotoxicity) – this is called a virtual cross match. 3. Those specificities would then be 'de-listed' as unacceptable on the UK waiting list, thus allowing the offer of a kidney with one or more previously unacceptable HLA types. 4. By removing some unacceptable HLA specificities the patient's cRF would necessarily reduce. This is the only point relevant to the management of the waiting list – NHSBT would need to take a position as to whether the patient remained listed with their original cRF or modified cRF. **KOS itself would not need to be modified**. 5. The HLA type of deceased donors is known some time (often very many hours) before organ retrieval, and therefore organs offered before retrieval. Thus a patient listed with the expectation of receiving Imlifidase would be offered a kidney and admitted to the transplant centre before organ retrieval. As soon as the organ was retrieved and determined anatomically suitable then Imlifidase could be administered. 6. Often several hours elapse before the organ arrives at the transplanting centre. During this time patients often require dialysis. 7. A post-Imlifidase 'cross match' would be needed. In practice, in the UK, this is likely to be an HLA antibody assessment using Luminex as opposed to a cellular cross match (a virtual cross match). Such testing takes 3-4 hours, and does not require donor cells.

		8. Thus the whole pathway, including administration if Imlifidase and subsequent HLA antibody assessment would take <12 hours, Assuming theatre availability then there would not necessarily be a detrimental effect on cold ischaemic time. 9. The ERG raises the issue of a second Imlifidase dose – occasionally needed for patients with very high (cytotoxic) DSA levels. We believe that most UK units would not attempt to overcome cytotoxic DSA levels with Imlifidase, and that consequently the requirement for a second dose is likely negligible.
Key issue 3: Generalisability of the evidence to NHS contexts	**NO**	In some ways this is the essential point. Imlifidase will be indicated for a small number of wait-listed patients – similar to those in the small trials discussed. Just as it would be impossible to conduct an RCT in this patient group, so is it hard to generalize the use of Imlifidase for this indication to the wider NHS. Instead the use of Imlifidase is specifically targeted at a group of patients for whom existing NHS treatment (a successful transplant) is effectively denied.
Key issue 4: Interpretation of treatment outcomes following transplant	**NO**	We agree with the ERG that extrapolating long-term outcomes (graft and patient survival, quality of life) is difficult from the small and short-term clinical experience currently available. We also agree with the Company submission that using the iBox methodology is reasonable and sensible, and that acceptable long-term (5 and 10 year) outcomes are realistic. Much depends on patient selection. We believe that, rather than requiring further trial data (which would necessarily be limited), a practical option would be to employ the 'Commissioning through Evaluation' approach available within NHSE specialized services. This would allow for a controlled introduction of Imlifidase in the NHS, and harness the very great strengths of transplantation in the UK – a national service with an established central listing and organ allocation organization (NHSBT), robust national data collection, and an excellent pedigree in national clinical trials – for example the 3C Study (Lancet (2014) 384, 1684-90)
Key issue 5: Comprehensiveness of the clinical evidence base	**NO**	Response as for Key Issue 4

Key issue 6: Comparators in the economic model	**NO**	As we have outlined above (Key Issue 1), the reality is that the majority of highly sensitized patients wait for many years for the offer of a compatible kidney, and inevitably become dialysis dependent. The ERG assessment frequently refers to the additional cost of performing a cross match following Imlifidase treatment – either a cellular cross match (flow cytometry or CDC) or a virtual cross match using an HLA antibody screen. In neither case is the cross match tests an additional cost – almost all very highly sensitized patients would require a cross match (cellular or virtual) even if offered a compatible kidney.
Key issue 7: Quality of life data used in the economic model	**NO**	Data on this point is very limited.

Additional issues [Delete this section if not responding to any other issues]

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Adjunctive treatments	Section 4.2.8.4, page 77	**NO**	Clinical experience with Imlifidase has used induction immunosuppression with agents including anti-CD20 antibody, alemtuzumab, and equine anti-thymocyte globulin. None of these are currently recommended by NICE or commissioned by NHSE. Commissioning of Imlifidase would require limited commissioning of these agents
Additional issue 2: HLA antibody testing	Section 2.3, page 26	**NO**	The ERG document frequently refers to the frequency of HLA antibody screening – with testing frequency as low as once yearly, and perhaps monthly in Imlifidase-treated patients. The clinical reality in the UK is entirely different. For these highly sensitized patients HLA antibody screening will be both frequent and equivalent for both those receiving a compatible kidney (to ensure that they do not develop new DSA), and for Imlifidase-treated patients (to monitor DSA rebound).
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Monday 11 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS Blood and Transplant – Organ and Tissue Donation and Transplantation**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Relevance of comparators and methodological uncertainty	No	In the UK currently there is an insufficient supply of organs (c. 5000 active on the renal transplant waiting list and 3000 transplants annually). Any organ used in this fashion with imlifidase could be used for someone else in a much cheaper fashion, with better outcomes and equal cost savings related to dialysis avoidance. Whilst from an individual patient perspective it may seem desirable it is difficult to see any cost savings delivered to the overall healthcare system.
Key issue 2: Placement of imlifidase in the UK treatment pathway	No	The current system was reconfigured in 2019 to increase access to highly sensitised patients. There is already evidence that this change is delivering more transplants to Tier A patients (CRF =100, > 7 years wait or Matchability score of 10). I am not sure that the Kidney offering scheme would need to be altered if imlifidase were to be used since individual centres would remove unacceptable antigens resulting in allocation. There would need to be some control and agreement on when this should take place.
Key issue 3: Generalisability of the evidence to NHS contexts	No	The existing patients were all treated in the USA and continental Europe. The principles should be applicable to a similar healthcare system in the UK
Key issue 4: Interpretation of treatment outcomes following transplant	No	The treatment regime is very intensive with significantly intensified immunosuppression (Alemtuzumab, Rituximab, Imlifidase, IvIGs in addition to triple therapy). There must be some concerns over the long term safety of such

		regimes and the studies have only relatively short follow up periods. One of the US patients (Lonze et al.) had severe antibody mediated rejection treated with bortezomib, eculizumab and medical splenectomy. This would be very unusual in the UK and would be extremely expensive.
Key issue 5: Comprehensiveness of the clinical evidence base	No	There is relatively short follow-up on the patients who have had imlifidase and longer term data (renal function, proteinuria and protocol biopsy data) is not clear
Key issue 6: Comparators in the economic model	**N**o	This could be resolved by the company only charging for drug when the transplant proceeded
Key issue 7: Quality of life data used in the economic model	No	There is no data on quality of life

Additional issues [Delete this section if not responding to any other issues]

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

lifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

A Single Technology Appraisal

ERG Review of Company's Response to Technical Engagement Response

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Produced by

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Rider on responsibility for document The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This TE response is linked to ERG report Farmer C, Knowles E, Kiff F, Long L, Robinson S, Nikram E, Powell R, Moore J, Griffin S, Hatswell A, Crathorne L, Melendez-Torres G.J. lifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2020.

1. INTRODUCTION

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of imlifidase for preventing kidney transplant rejection in people with chronic kidney disease (ID1672).

The company did not provide any further evidence towards this appraisal; however, the company accepted a number of the ERG preferences in their revised base case. The ERG critique of the company's revised analyses and the preferred ERG base case is presented in Section 2. The company provided a series of narrative responses to the remaining key issues raised by the ERG; in all cases, these issues were addressed by the ERG during the factual accuracy check, and the ERG view remains unchanged. However, the ERG has provided a brief response to each key issue in Section 3.

2. UPDATED COMPANY ALTERNATIVE ERG BASE CASE ANALYSES

2.1. Summary of updated company and ERG base case analysis

In response to technical engagement, the company did not present any new evidence to support the submission though several of the ERG's preferred assumptions were accepted by the company, listed below:

1. ERG error corrections (ERG report, Section 5.1.1.)
2. Implement caregiver disutility from Thomas *et al.*[45] (ERG report, Section 6.3.5.**Error! Reference source not found.**).
3. Apply caregiver disutility to 90% of haemodialysis patients compared to 100% in the company's base case (ERG report, Section 6.3.5.**Error! Reference source not found.**).
4. Redistribute the distribution of hospital-paid transport to exclude 'ambulance' (ERG report, Section 6.3.6.**Error! Reference source not found.**).
5. Include the cost of one crossmatch test following each full dose of imlifidase (ERG report, Section 6.3.7.**Error! Reference source not found.**).
6. Use the average patient weight obtained from the clinical trials throughout the model (ERG report, Section 6.3.8.**Error! Reference source not found.**).
7. Include the cost of DSA test (three antigens) annually for transplant patients and at time of graft loss (ERG report, Section 6.3.12.**Error! Reference source not found.**).

Furthermore, the company made the following amendments to their base case which incorporate the ERG's critiques (though with different values), and are discussed in further detail in Section 3:

1. Application of 97.9% of patients (45/46) administered imlifidase to receive a subsequent transplant (100% in the company's original base case) I.e. an ITT perspective
2. Allow 1.0% of dialysis patients to receive a transplant (0% in the company's original base case).

In addition to the updates listed above, the company identified an error in the ERG's application of the dialysis status distribution of patients in the company model (ERG preferred assumption 3) which has subsequently been rectified by the ERG and reduces the ERG's ICER from approximately £95,000 per QALY, to £87,000 per QALY.

The updated base case results for the company and ERG (error corrected) are presented in Table 1.

Table 1: Company and ERG base case results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*33,657*
ERG base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*87,920*
Company base case (probabilistic)							
Imlifidase	[redacted]	-	[redacted]				
Dialysis	[redacted]	-	[redacted]	[redacted]	-	[redacted]	*31,948*
ERG base case (probabilistic)							
Imlifidase	[redacted]	-	[redacted]				
Dialysis	[redacted]	-	[redacted]	[redacted]	-	[redacted]	*89,999*

3. ERG REVIEW OF KEY ISSUES

The ERG response to each of the key issues addressed in the company's technical engagement response is provided in Table 2. A detailed response to Issue 6 and Issue 7 is provided below.

Table 2: ERG review of company response to key issues

Key issues	Summary of issues	ERG Report sections	ERG response to TE
Error! Reference source not found.	Relevance of the comparator: should the appraisal consider the costs and benefits of kidney transplant in those not eligible to receive imlifidase	**Error! Reference source not found.**; **Error! Reference source not found.** – **Error! Reference source not found.**; **Error! Reference source not found.** – **Error! Reference source not found.**; **Error! Reference source not found.**– **Error! Reference source not found.**	The view of the ERG remains unchanged. The ERG agree that the availability of imlifidase may provide more equal access to kidney transplantation for some patients who cannot at present be matched with a donor. However, in determining the cost-effectiveness of imlifidase, to fully account for costs and benefits, given the scarcity of kidneys (with demand exceeding supply and a waiting list), it may be appropriate to consider the costs and benefits forgone by another patient (who may or may not be highly sensitised) receiving the kidney without the use of imlifidase. This approach is not taken in the ERG basecase, as the ERG believes that the question of scope is for the committee to decide.
Error! Reference source not found.	Placement of imlifidase in the UK treatment pathway: how would the treatment pathway change, and would changes to the Kidney Offering Scheme be necessary	**Error! Reference source not found.** - **Error! Reference source not found.**; **Error! Reference source not found.**;	The view of the ERG remains unchanged. The ERG still consider there to be some uncertainty about the impact of imlifidase on the treatment pathway and kidney allocation scheme, and that further input from stakeholders would be useful. The ERG note that stakeholder responses to technical engagement highlight the uncertain nature of how the technology would be introduced.

Key issues	Summary of issues	ERG Report sections	ERG response to TE
		Error! Reference source not found.; **Error! Reference source not found.**	
Error! Reference source not found.	Generalisability of limited evidence to NHS contexts: assumptions about the outcomes that would occur absent the drug limit generalisability to the UK population	**Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**	The view of the ERG remains unchanged. The ERG recognise that the company has presented all available evidence, and note that in their response to technical engagement the company state that they were unable to conduct a matched comparison within the available evidence. The ERG stated that as relative treatment effects cannot be estimated from the trials, the company's assertion of effectiveness relies on an implicit assumption that absent the drug, specific outcomes (such as negative crossmatch tests) would not have been observed. Specifically in response to the example given, the company state that there is no biological process through which a negative crossmatch may occur spontaneously. This may be the case; however the ERG point was regarding the uncertainty over the proportion of patients who will find a negative crossmatch with a donor. This unknown has caused considerable uncertainty in the CS more broadly. While the disease mechanism relevant to the appraisal may be consistent across centres and geographical areas, the ERG maintain that the lack of an available clinical definition of the target population, and the use of different treatment protocols, may nevertheless impact the clinical- and cost-effectiveness of imlifidase.
Error! Reference source not found.	Interpretation of treatment outcomes: lack of comparative data restricts interpretation of the clinical significance of observed effects	**Error! Reference source not found.**; **Error! Reference**	The view of the ERG remains unchanged. The ERG consider that the evidence presented by the company does not resolve uncertainty about the potential short- and long-term outcomes of kidney

Key issues	Summary of issues	ERG Report sections	ERG response to TE
		source not found.; **Error! Reference source not found.**; **Error! Reference source not found.**	transplantation in the target population.
Error! Reference source not found.	Comprehensiveness of the clinical evidence base: significant gaps in the clinical evidence base limit understanding of the efficacy and safety of imlifidase, and its place in the treatment pathway	**Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**	The view of the ERG remains unchanged. The ERG are disappointed that the company did not use this opportunity to provide the clinical effectiveness data in a way that would have given greater confidence in the findings. As a consequence, the ERG cannot fully validate the clinical effectiveness estimates.
Error! Reference source not found.	Comparators in the economic model: the company's model includes only those patients who were successfully treated with imlifidase, and thus received a transplant	**Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.** - **Error! Reference source not found.**	The view of the ERG remains unchanged, with the company accepting the ERG's change to an ITT perspective i.e. including all patients who received imlifidase, regardless of transplant outcome. The company identified an error in the ERG's application of the dialysis status distribution which has been rectified. An addendum to the ERG report has been provided with corrected results.
Error! Reference source not found.	Quality of life data used in the economic model: no quality of life data have been collected for patients who have received imlifidase	**Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference**	The view of the ERG remains unchanged. No directly collected data is available from the patient population, and the impact of transplant is unclear. The ERG have identified recently published evidence that details the impact of a transplant in individuals (rather than comparing between groups with different patient characteristics)

Key issues	Summary of issues	ERG Report sections	ERG response to TE
		source not found.; **Error! Reference source not found.**	which reduces, but does not eliminate, the uncertainty regarding the effect in the patient population.

3.1. Issue 6: Comparators in the economic model

The company made two amendments following technical engagement (TE) to the population considered in the economic model for this appraisal:

1. Allow a proportion of imlifidase patient to be unable to receive a subsequent transplant
2. Allow a proportion of comparator patients to recieive a transplant

The amendments to the company base case are discussed seperately below.

3.1.1. Imlifidase patients unable to receive a transplant

In the company's original base case assumptions, the proportion of imlifidase patients assumed to go on to receive a transplant was 100%. The ERG felt this approach was unrepresentative of reality as it is likely that some patients may not receive a transplant following imlifidase administration (as seen in the clinical studies). The ERG's base case incorporated data from the clinical trials in which 2 out of 54 patients discontinued imlifidase prior to transplantation, thus the propotion of patients to receive a transplant in the imlifidase arm was set to 96.3%. Furthermore, one out of 52 remaining patients did not achieve a negative FACS crossmatch (the outcome of the trial) however, received a subsequent transplant nonetheless. Therefore, the ERG presented a scenario where the proportion of patients to receive a transplant in the imlifidase arm is informed by those who received a full dose multiplied by those who achieved a negative crossmatch, resulting in 94.4%.

Following TE, the company revised the original estimate of 100% to 97.9% which is obtained from 45 out of 46 patients in trials excluding Study 02 successfully receiving a transplant. The ERG disagree with the exclusion of Study 02 as while the key trial outcomes did not include transplantation, the evidence remains that one patient in the study was discontinued due to adverse events. With limited patient numbers, the ERG's view is unchanged and makes no adjustment to the preferred base case assumptions.

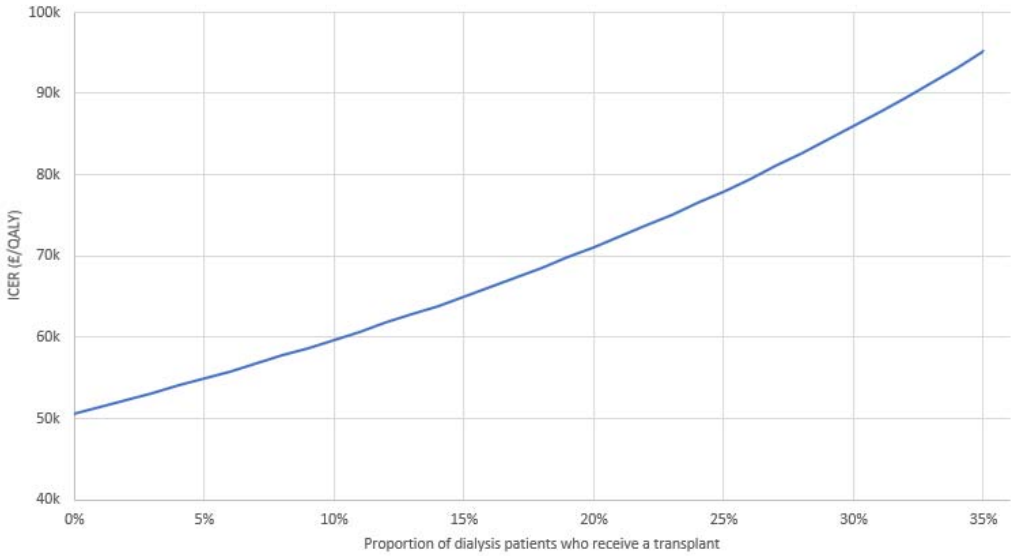
3.1.2. Comparator patients able to receive a transplant

In the company's original base case, the proportion of patients in the comparator arm assumed to received a transplant over a lifetime horizon was 0%. The ERG registered its concerns with this approach and presented a preferred assumption in which 31.44% of dialysis patients were assumed to receive a transplant, in order to reflect that some highly sensitised dialysis patients would receive a transplant without imlifidase. The estimate of 31.44% was derived from data obtained from NHSBT and is described fully in the ERG report, Section 6.3.2 which gives the rate over the past 5 years for a ≥99% cRF population. Due to the model structure, the comparison is somewhat limited as patients cannot move between the dialysis and transplant health states, therefore, all patients estimated to receive a transplant are assigned to transplant in cycle 0; i.e. the probabilities over the first few years are summed.

Following TE, the company revised its original estimate of 0% to 1% in order to capture a small number of patients receiving a transplant without imlifidase. The company highlights in its response to TE that the population of interest for this appraisal is difficult to outline, with a protocol for UK practice yet to be defined. While agreeing that the true comparator cannot be identified, the ERG believes the data obtained from NHSBT for the ≥99% cRF patients remains the best proxy presented so far in this appraisal to inform the proportion of patients who would receive a transplant without imlifidase. Therefore, the ERG's base case remains unchanged. However, the ERG recognise the limitations of this assumption, with the exact rate likely to be determined by the characteristics of the patient population who would be treated—a population that remains unclear and undefined.

For completeness Figure 1 presents the ICER as the proportion of patients assumed to receive a transplant in the comparator arm varies. This is calculated using the ERG's base case assumptions. It can be seen that using the 1% rate proposed by the company, or the 4% rate suggested by clinical responses to technical engagement (which we believe to be an annual rate, rather than a lifetime rate), the ICER remains over £50,000 per QALY.

Figure 1: Effect of the proportion of patients in the comparator arm to receive a transplant on the ERG's base case settings



3.2. Issue 7: Quality of life data used in the economic model

In terms of the quality of life impact of transplant, the longitudinal values used by the ERG are important, as they consider the impact a transplant has had on a patient, rather than comparing values between groups who did, and did not receive transplant. This is as when comparing groups, the patients are also likely to differ in a number of other important factors (such as age, and comorbidities). This can be seen in the meta-analysis of utility values used in the original company submission where the mean age of transplant patients is approximately 10 years younger than dialysis patients (shown in Table 2) and is stated by the authors of the paper:

When assessing studies using preference-based methods, renal transplantation (RTx) is associated with a higher quality of life than either hemodialysis (HD) or peritoneal dialysis (PD). Nevertheless, other authors suggested that this might be due to pre-existing different characteristics of patients selected for the alternative forms of RRT, such as age, sex, ethnicity, primary renal disease, and comorbidity.[1]

4. ERG CRITIQUE OF ADDITIONAL EVIDENCE

No additional evidence was provided by the company at the technical engagement stage.

5. REFERENCES

1. Liem YS, Bosch JL, Hunink MGM. Preference-based quality of life of patients on renal replacement therapy: A systematic review and meta-analysis. *Value Health* 2008; **11:** 733-741.

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Addendum #1: Revised Section 6 ERG Report (post TE response)

January, 2021

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INTRODUCTION

The purpose of this addendum is to provide the updated ERG report Section 6 following edits made in response to technical engagement. Note that cross references link to the ERG report (date 12/11/2020, post FAC).

EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Data received from NHSBT

The population of interest in this appraisal, "those unlikely to receive a transplant under the existing protocols of the KOS", are a poorly defined group, with little information provided by the company on the outcomes and treatment patterns seen in NHS practice. For example, the split of dialysis modalities used in the economic model by the company was obtained from the whole waiting list population in the 21st annual UKRR report.[49]

To this end, the ERG requested data from NHSBT[53] to better inform the model. In order to operationalise the definition of "highly unlikely", the ERG requested data from NHSBT[53] where patients were grouping by their degree of sensitisation; all patients, ≥85% CRF (referring to the traditional definition of highly sensitised), and ≥99% sensitised (reflecting a group of patients highly unlikely to match to any individual kidney). The ERG would like to place on record its thanks to NHSBT for their rapid and extremely helpful responses to our queries.

Though the patient group detailed by the company suggests immunological factors other than CRF are also likely to affect a patient's chance to receive a match, the ERG believed that in the absence of a full definition or alternative data source, the data provided by NHSBT[53] for the CRF ≥99% group provide a reasonable proxy to the population of interest for this appraisal. Furthermore, the ERG believed the data to relate more to the population of interest than the figures reported by the company from the 21st annual UKRR report.[49]

6.2 Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a number of additional exploratory and sensitivity analyses, which are summarised below:

- In order to explore an ITT population for the intervention arm, the ERG implemented an analysis where a proportion of patients received imlifidase but did not go on to achieve a negative crossmatch, and consequently, did not receive a transplant. This proportion was varied within the sensitivity analysis to explore the impact on the model results.
- The ERG analysis assumes that a proportion of highly-sensitised patients in the comparator arm will receive a transplant without imlifidase treatment. Data obtained from

NHSBT[53] in the relevant patient population was used to populate this proportion, which was varied for sensitivity analysis.

- Data from NHSBT[53] revealed that not all patients on the transplant waiting list (in the whole population, and in the highly sensitised population) are receiving dialysis treatment. The ERG applied the distribution of dialysis status provided by NHSBT within the analysis for the patient group of interest (with the split of haemodialysis patients taken from the UKRR 21st Annual Report). The ERG was also unable to validate the proportions for the types of dialysis used in the company base case therefore alternative proportions obtained from Table 2.6 of the UKRR 21st Annual Report[49] were applied in sensitivity analysis.
- The ERG considered a recently-published utility study by Cooper *et al.*[44] as a better proxy to inform the utility values in the cost-effectiveness model due to the methodological quality, but also year of searches (2020 vs 2006). The ERG implemented these values for the analysis, with values taken from Li *et al.*[43] explored in sensitivity analysis.
- The ERG applied an alternative caregiver disutility with better methodological validity to haemodialysis patients, and reduced the proportion of patients expected to have a caregiver to explore the impact on the model results.
- The ERG was concerned with the high cost assigned to haemodialysis travel by 'ambulance' in the company's analysis (>£200 for every 5th visit), and the effect on the ICER. The ERG considered an alternative approach by redistributing the proportion of patients from this transport to other NHS-cost incurring options.
- The ERG believed the omission of crossmatch tests following each full dose of imlifidase to be incorrect, and therefore have included the cost of crossmatch testing after every infusion of imlifidase.
- The average patient weight used by the company for the calculation of other drug costs (i.e. not imlifidase) was not taken from the clinical trials. The ERG has opted to implement the clinical trial average weight (i.e. the same as imlifidase) in order to more accurately reflect the patient population and be consistent in calculations.
- The ERG was concerned that the iBox predictive model was developed in a population with a different proportion of previous transplants compared to the population considered in the model. As previous transplant is a prognostic factor, the ERG has explored the impact of applying a relative risk to the iBox predictions.

- The ERG applied an increased cost for transplant to account for organ retrieval and transportation.
- The ERG considered that only a finite number of donor kidneys are available, and has therefore conducted a scenario analysis where the transplant is provided to patients who are not considered 'highly-sensitised' and thus, do not require imlifidase treatment.
- The ERG was concerned that DSA testing costs have not been captured in the model, therefore an analysis is conducted where DSA tests are applied once annually as transplant maintenance and at the time of graft loss.

6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The analyses described in Section 6.2 are described in turn within each section below. The impact on the ICER described below refers to the company's base case ICER including the ERG corrections detailed in Section 5.2.

6.3.1 Patients receiving imlifidase but unable to progress to transplant

As discussed in Section 4.2.4 and Section 3.2.4, while imlifidase appears to be efficacious, there is uncertainty in the rate of crossmatch conversion from positive to negative. Although the rate is clearly high, one patient failed to achieve a negative FACS crossmatch (and received a transplant regardless as a negative virtual crossmatch result was achieved and clinical judgement supported the procedure), with two further patients having adverse reactions to imlifidase and were unable to receive a full dose (and subsequent transplant). As such the ERG has adapted the company's model to allow a proportion of patients to receive imlifidase but not to undergo transplantation. As the true rate of crossmatch conversion is unknown the ERG has adjusted the proportion to receive transplant in the intervention arm by accounting for the patients who did not receive the full dose. Furthermore, in a scenario analysis, this proportion is also adjusted to account for the patient who did not achieve a negative FACS crossmatch. This resulted in a rate of transplant for the imlifidase arm of 96.3% in the ERG base case and 94.4% in a scenario analysis as opposed to the 100% in the company submission. This is consistent with the clinical findings where the high rate of crossmatch conversion was also subject to uncertainty.

Decreasing the proportion of imlifidase patients to receive a transplant from 100% to 96.3% resulted in an increase of £2,488 to the ICER (£31,971 to £34,459). Alternative proportions

including the scenario to account for the failed conversion to a negative FACS crossmatch are explored in scenario analysis in Section 6.4.1.1.

6.3.2 Likelihood of receiving transplant without imlifidase

The economic model submitted by the company does not allow for any patients on dialysis to receive a transplant at any point in their lifetime. The ERG highlights concern with this approach in Section 4.2.4. In order to reflect that some (though not all) highly sensitised dialysis patients would receive a transplant without treatment with imlifidase, the ERG conducted the following additional analyses:

- Inclusion of an additional ERG comparator ('dialysis and transplant') where a proportion of dialysis patients receive a transplant.
- Heatmap combining the assumed proportion of dialysis patients to receive a transplant and the assumed proportion of imlifidase patients to receive a transplant.

The ERG noted that the 'dialysis and transplant' comparator only provides a limited comparison between the treatment arms as, due to the model coding, patients were assigned to either dialysis or transplant at Cycle 0. In practice it is expected that patients are likely to remain on dialysis prior to a suitable transplant becoming available – however, as patients cannot transition from dialysis to transplant in the model, no dialysis costs can be accrued prior to transplant to reflect the expected delay in receiving a transplant.

With this limitation in mind the ERG was able to perform the comparison using data provided by NHSBT[9] for years 2015 to 2019. The data showed that 119 transplants occurred for the ≥99% cRF group in the year 2019/2020 (the first full year of the revised KOS), with a mean of 77 transplants performed in the same patient group over the previous four years (2015/2016 - 2018/2019). As of 30 September 2020, there were 495 highly-sensitised patients with a cRF of ≥99% on the transplant waiting list. The 119 patients who received a transplant in the 2019/2020 year corresponds to 24.0% of 495 patients on the waiting list.

In reality, the ERG expects the number of transplants received in the 2019/2020 year to likely be inflated due to a backlog of highly sensitised patients who were suddenly assigned a higher weighting in 2019 as a result of the revised KOS. As such, the mean number of transplants over years 2015 to 2019 (85) was used to calculate an expected proportion of highly sensitised dialysis patients who would receive a transplant without treatment with imlifidase. This provided

an annual probability of 17.2% (85/495). Due to the confines of the model structure, it was assumed that patients would remain fit enough for transplant for two years from model entry, following which they would become ineligible in keeping with clinical input to the ERG that eventually patients would become too sick to be transplanted. This provided a proportion of 31.4% of patients who could expect to receive a transplant in the comparator arm.

The ERG noted that due to the limitations of the model, the patients who undergo transplant in the comparator arm would incur slightly different costs in reality, as the rate of transplant would be effectively spread over time, as opposed to all occurring at Cycle 0 in the model. This unfortunately is a limitation of the model coding, but is not expected to radically change the results and represents, along with the duration for which patients may be able to undergo a transplant, a limitation.

Furthermore, clinical opinion to the ERG indicated that DSA monitoring is likely to be more frequent for patients who undergo an HLA incompatible transplant. Therefore, the ERG has applied DSA costs; monthly for the first 6 months, once every two months for 7-12 months and once annually thereafter following transplant for the patients receiving a transplant without imlifidase treatment. DSA costs are further discussed in Section 6.3.12.

Allowing 31.44% of dialysis patients to receive a transplant resulted in an ICER change from £31,971 to £59,335.

6.3.3 Changing the comparator to established clinical management, from dialysis

As discussed in Section 4.2.4, the company's economic model assumed all non-transplant patients receive dialysis. However, data provided by NHSBT[9] in the highly sensitised group (≥99%), showed that some patients are not currently on any dialysis treatment (77/491, 15.7%), with the remainder receiving haemodialysis (366/491, 74.5%) and peritoneal dialysis (48/491, 9.8%). Clinical input to the ERG agreed with this finding, with the explanation that a proportion of patients are listed for transplant pre-emptively – i.e. when eGFR <15 but still with enough kidney function to not require dialysis, whilst other patients are those with failing grafts who again maintain sufficient kidney function to be dialysis free, but do require transplantation (i.e. relisting).

To reflect the NHSBT data, the ERG implemented the proportions of patients to receive each dialysis modality (including no dialysis) in their base case analysis as taken from the NHSBT data. As the split of haemodialysis was not available from NHSBT, the proportion of patients assigned to hospital, satellite and home haemodialysis was obtained from the UKRR 21st Annual Report. The ERG understand it is likely that all patients may receive dialysis at some point however, particularly as patients age. It is therefore assumed that after the first two years, all patients will move to dialysis in the proportions seen in the NHSBT data (88.4% haemodialysis and 11.6% peritoneal dialysis). The ERG acknowledges this assumption (i.e. a maximum two years without dialysis) to be a limitation of the analysis however believe in the absence of data, it represents a plausible value, which can be changed based on data or expert opinion should the committee wish.

A further limitation is that as there is a lack of available data to inform overall survival for the patients not on dialysis, overall survival was assumed to follow the same trajectory as those on dialysis in the model. This assumption may result in an underestimate of the effectiveness of the comparator arm as it is likely these patients are healthier than those who are on dialysis i.e. they are earlier in the disease pathway.

Changing the comparator to reflect established clinical management represented an increase in the ICER from £31,971 to £32,828.

6.3.4 Utility values used for patients in the model

Using data from the recently published meta-analysis from Cooper *et al.*[44], and assuming 25% of patients are aged over 65 years (in line with the clinical studies), the ERG calculated that using longitudinal estimates, pre-transplant patients had a mean utility of 0.7385, which increased to 0.84 a year after transplant (the timepoint measured in the studies). For simplicity these values were used pre-/post-transplant, with age adjustments then applied throughout the model time horizon using the decrements from Table A of Kind *et al*[46].

These longitudinal values are important, as they consider the impact a transplant has had on a patient, rather than comparing values between groups who did, and did not receive transplant. This is as when comparing groups, the patients are also likely to differ in a number of other important factors (such as age, and comorbidities).

Using Cooper *et al.*[44] as the utility source resulted in an increase of £6,701 to the ICER (£31,971 to £38,672).

6.3.5 Utility values used for carers in the model

As discussed in Section 4.2.7, a carer disutility of 0.03 was applied for patients in receipt of haemodialysis. The ERG anticipated that not all haemodialysis patients would have a caregiver and so applied a caregiver utility to 90% of haemodialysis patients (rather than 100% in the company's base case), with 100% of patients explored as a scenario analysis.

Incorporating a 0.03 utility decrement to account for caregivers of haemodialysis patients results in a reduction of £541 (£31,971 to £31,431). Reducing the proportion of patients with a caregiver from 100% to 90% resulted in an increase of £38 to the ICER (£31,971 to £32,009)' to put them separately.

6.3.6 Cost of patient transport

The cost of patient ambulance transport used by the company (£219) is extremely similar to that of an emergency in NHS reference costs 2018-2019[54] (ASS02 See and treat and convey, £257), and is in reality likely to be a (shared) community ambulance. Furthermore, it is not clear other costs (such as taxis) need inflating given changes in the transport market over time to make it more competitive (such as the increase in ride hailing apps, and changes in transport patterns) – with 10 years since the data used was collected.

Due to this uncertainty and the absence of suitable costs, the has ERG redistributed the 18% from ambulance to the other NHS-incurred travel costs. Table 18 presents the proportion of haemodialysis patients assigned each mode of transport in the company analysis, and the reweighted proportions preferred by the ERG.

Table 18: Comparison of haemodialysis transport in company and ERG analyses

Transport	**Company**	**ERG**
Ambulance service vehicle	18%	0%
Hospital provided car	12%	16.7%
Hospital arranged taxi	12%	16.7%
Hospital transport vehicle	22%	30.6%
Public or private transport	36%	36%

Abreviations: ERG, Evidence Review Group

Applying the ERG's reweighted proportions saw an increase of £5,114 to the ICER (£31,971 to £37,085). The ERG note however that this input is subject to substantial uncertainty, and further data could provide a better understanding of the true costs to the NHS of patient transport.

6.3.7 Cost of crossmatch tests

The company does not apply any costs associated with crossmatch testing in the model. The ERG has discussed concerns with this approach in Section 4.2.8.1.

In order to capture the costs of crossmatch testing for the analysis, the ERG applied a cost of £300 following each full dose of imlifidase received. The ERG was unable to find the cost of one FACS crossmatch test (FACS crossmatch tests were used in the clinical studies) alone however, the cost of one FACS test with one CDC test was reported in the literature[51] and so, to account for just one test being used, the ERG has halved this cost and implemented this in the model.

Applying crossmatch test costs within the model results in an increase of £78 to the ICER (31,971 to £32,049), though further information would be able to resolve this uncertainty.

6.3.8 Patient weight

The ERG found the company to have taken the average patient weight of 75 kg applied in the model from a Welsh study in 2009.[55] The ERG found the average weight of patients in the 'all imlifidase' patient group to be 69 kg and so have applied this in a sensitivity analysis for consistency with the costing of imlifidase (which uses actual patient weights). Using the average patient weight from the clinical studies resulted in an increase of £29 to the ICER (£31,971 to £31,942).

6.3.9 Survival post transplant in a highly pre-treated patient population

The ERG noted that the patient population in the highly sensitised group will potentially have worse outcomes than a 'standard' transplant population for four reasons:

- The increased CIT *ceteris paribus* when imlifidase is required to enable a transplant;
- The presence of antibodies against the donor kidney;
- The increased length of time these patients will likely have spent on dialysis;

- The number of patients who have had a prior transplant, compared to the iBox population on which estimates were based (and in which no coefficient is described for prior transplant).

Although it was not possible to quantify these concerns, the ERG provided a sensitivity analysis where a hazard ratio of 0.95 is applied to the post-transplant survival, to understand the importance of long-term survival. This change increased the ICER by £1,426 (£31,971 to £33,397)

6.3.10 Transplant costing

According to the NHSBT Activity report 2019/20[56] there were 3,760 organ transplants in the UK with a net expenditure of NHSBT of £79.9 million[4], which gives a crude cost per organ of £21,010. As the organ for any transplant has to be provided – including managing donor lists, liasing with families, retreiving organs, and transporting them under tight time windows, these costs should be included within the appraisal to be consistent with the NICE methods guide (the inclusion of all relevant costs and benefits). As such the ERG presented a scenario including this cost for transplant.

It should be noted that this cost is applied for any transplant (including in the comparator arm). The ERG acknowledged it is also likely that the cost per organ is not likely to be the same for all organs and donor types; as such improved estimates of cost may be helpful, if available. Including this cost increased the ICER from £31,971 to £33,583.

6.3.11 Reflecting the opportunity cost of a donor kidney

As discussed in both the CS and ERG report, donor kidneys are scarce with the waiting list evidencing that demand exceeds supply. As with the principle of cost-effectiveness where money not spent on an intervention will be spent elsewhere in the system, any kidneys not received by imlifidase patients would be received by other patients; i.e. imlifidase will not increase the number of kidneys available to transplant.

This question is one of the scope of the appraisal, and a question which is not covered by the NICE scope, or anticipated by the NICE methods guide (though the reflection of all costs and benefits might indicate that the opportunity [health] cost of the kidney be included).

In order to explore the impact of this opportunity cost, a comparison was made by the ERG of giving a kidney to an imlifidase patient vs to a patient not requiring imlifidase (who may or may not be in the >99% sensitised group). Although limited in its application, this scenario showed the use of imlifidase to be dominated; using a threshold of £30,000 per QALY the ERG found a net benefit of [redacted] / net health benefit of [redacted] QALYs.

6.3.12 DSA testing

As discussed in Section 4.2.8.5, no costs associated with DSA testing are applied within the model. Clinical advice to the ERG indicated that in HLA-incompatible transplants DSA monitoring would indeed be administered more frequently than with an HLA-compatible transplant. As imlifidase induces a negative crossmatch by depleting the antibodies, an HLA-compatible transplant can be performed. Although these antibodies are likely to rebound following transplant, clinical advice to the ERG was conflicting on whether additional DSA monitoring would be required for this population following imlifidase. The ERG was also unable to interpret the clinical outcome of HLA rebounds due to limited reporting in the CS (Section **Error! Reference source not found.**), which provided further uncertainty on the monitoring of DSAs post-transplant.

Clinical opinion was, however, in agreement that DSA testing would be implemented (as a minimum) when a graft failure is suspected. At clarification stage the company provided the cost for a DSA test on one antigen (£55) and stated clinical opinion was that three antigens of interest could be expected however, this could be between one and six antigens. The ERG explored the effect on the model results when including DSA tests for use in transplant maintenance (tested for three antigens, once annually) and at the time of graft failure. Therefore, the ERG applied the cost for three antigens (£155) at the time of graft failure as a scenario analysis in the model. DSA test costs are also applied in the ERG's base case for the comparator patients who go on to receive a transplant, further discussed in Section 6.3.2.

The inclusion of these costs resulted in an increase of £373 in the ICER from £31,971 to £32,344. The ERG noted, however, that it appears clinicians may perform more DSA testing than this, which represents an uncertainty about how imlifidase would be used in practice, and may be worthy of consensus being gained, and then implemented in modelling.

6.3.13 Overview results of exploratory and sensitivity analyses

An overview results of exploratory and sensitivity analyses is provided in Table 19.

Table 19: Exploratory and sensitivity analyses

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's base case	[redacted]	[redacted]	*£30,641*
ERG error fixes			
Apply 0-6 month transplant maintenance costs	[redacted]	[redacted]	*£31,953*
Apply imlifidase and transplant AE's to all imlifidase	[redacted]	[redacted]	*£30,683*
Apply caregiver disutility to Li et al. *(2017)[43]**	[redacted]	[redacted]	*£30,641*
Apply AE Cycle 5+ costs to transplant AEs	[redacted]	[redacted]	*£30,618*
Company corrected base case	[redacted]	[redacted]	*£31,971*
Scenarios below include the four ERG error fixes above			
Reduce the proportion of imlifidase patients to receive transplant – 96.3%	[redacted]	[redacted]	*£34,459*
Allow a proportion of dialysis patients to receive a transplant – 31.44%	[redacted]	[redacted]	*£59,335*
Apply NHSBT proportion of dialysis modality (including not on dialysis)	[redacted]	[redacted]	*£32,828*
Utility source – Cooper et al. *(2020)[44]*	[redacted]	[redacted]	*£38,672*
Caregiver disutility source – Thomas et al. *(2015)[45]*	[redacted]	[redacted]	*£31,431*
Reduce the proportion of HD patients with a caregiver to 90%	[redacted]	[redacted]	*£32,009*
Redistribute hospital-paid dialysis travel cost	[redacted]	[redacted]	*£37,085*
Apply crossmatch test cost per imlifidase dose	[redacted]	[redacted]	*£32,049*
Change average patient weight to 69 kg	[redacted]	[redacted]	*£31,942*
*Apply HR to iBox graft estimates – 0.95**	[redacted]	[redacted]	*£33,397*
*Apply alternative transplant cost - £21,000**	[redacted]	[redacted]	*£33,583*

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
*Change comparator to 'Non-sensitised transplant'**	[redacted]	[redacted]	*Dominated*
Include DSA test costs	[redacted]	[redacted]	*£32,344*
ERG base case	[redacted]	[redacted]	*£98,496*

Abbreviations: AE, Adverse event; DSA, donor-specific antibodies; ERG, Evidence Review Group; HD, haemodialysis; HR, Hazard Ratio; ICER, incremental cost-effectiveness ratio; kg, kilogram; NHSBT, National Health Service Blood and Transplant; QALY, quality-adjusted life year

Note:

*the base case analysis does not use the Li et al. (2017) utility values, hence no difference is observed in the base case ICER when including this correction

* Not included in the ERG base case

6.4 ERG's preferred assumptions

The ERG's preferred base-case analysis comprises several alternative model settings and assumptions:

1. Application of 96.3% of patients administered imlifidase to receive a subsequent transplant compared to 100% in the company's base case (Section 6.3.1).
2. Allow 31.44% of dialysis patients to receive a transplant compared to 0% in the company's base case (Section 6.3.2).
3. Application of the dialysis status distribution reported by NHSBT. Most notably this allows a proportion of patients in the comparator arm to receive no dialysis (Section 6.3.3).
4. Implement utility values taken from Cooper *et al.*[44] (Section 6.3.4).
5. Implement caregiver disutility from Thomas *et al.*[45] (Section 6.3.5).
6. Apply caregiver disutility to 90% of haemodialysis patients compared to 100% in the company's base case (Section 6.3.5).
7. Redistribute the distribution of hospital-paid transport to exclude 'ambulance' (Section 6.3.6).
8. Include the cost of one crossmatch test following each full dose of imlifidase (Section 6.3.7).
9. Use the average patient weight obtained from the clinical trials throughout the model (Section 6.3.8).
10. Include the cost of DSA test (three antigens) annually for transplant patients and at time of graft loss (Section 6.3.12).

11. 6.4.1 Summary of ERG's base case settings and assumptions

Despite the limitations highlighted within the company's model, the ERG determined a set of preferred settings and assumptions that are believed to represent a more plausible estimate of the cost-effectiveness of imlifidase. However, the ERG emphasised that several preferred assumptions such as the proportion of dialysis patients who were likely to receive a transplant without imlifidase and the amount of time comparator patients spend receiving no dialysis remain uncertain due to either model or knowledge limitations.

The ERG's preferred model settings and assumptions are summarised in Table 20. The individual and cumulative impact of each setting on the estimated ICER is presented alongside each change. The results presented are aligned with the base case results provided by the company, including equivalent settings.

Table 20: ERG's preferred model assumptions

Preferred assumption	**Section in ERG report**	**Individual change to corrected ICER £/QALY**	**Cumulative ICER £/QALY**
Company base case	*Section 5.1.1*	*-*	*30,641*
Company base case following ERG corrections	*Section 5.2*	*-*	*31,971*
Reduce the proportion of imlifidase patients to receive transplant – 96.3%	*Section 6.3.1*	*34,459*	*34,459*
Allow a proportion of dialysis patients to receive a transplant – 31.44%	*Section 6.3.2*	*59,335*	*64,592*
Apply NHSBT proportion of dialysis modality (including not on dialysis)	*Section 6.3.3*	*32,828*	*65,468*
Utility source – Cooper et al. *(2020)*[44]	*Section 6.3.4*	*38,672*	*79,558*
Caregiver disutility source – Thomas et al. *(2015)*[45]	*Section 6.3.5*	*31,431*	*80,971*
Reduce the proportion of HD patients with a caregiver to 90%	*Section 6.3.5*	*32,009*	*80,728*
Redistribute hospital-paid dialysis travel cost	*Section 6.3.6*	*37,085*	*87,349*
Apply crossmatch test cost per imlifidase dose	*Section 6.3.7*	*32,049*	*87,497*
Change average patient weight to 69 kg	*Section 6.3.8*	*31,942*	*87,462*

Preferred assumption	Section in ERG report	Individual change to corrected ICER £/QALY	Cumulative ICER £/QALY
Include DSA test costs	*Section 6.3.12*	*32,344*	*87,920*

Abbreviations: DSA, donor-specific antibodies; ERG, Evidence Review Group; HD, haemodialysis; ICER, incremental cost-effectiveness ratio; kg, kilogram; NHSBT, National Health Service Blood and Transplant; QALY, quality adjusted life year.

A comparison of the company's base case analysis and the ERG's preferred analysis results are presented in Table 21. The equivalent results of PSA using the ERG preferred assumptions are also provided.

Table 21: Comparison of company and ERG results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company original base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*30,641*
ERG base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*87,920*
Company original base case (probabilistic)							
Imlifidase	[redacted]	-	[redacted]		-		
Dialysis	[redacted]	-	[redacted]	[redacted]	-	[redacted]	*31,948*
ERG base case (probabilistic)							
Imlifidase	[redacted]	-	[redacted]		-		
Dialysis	[redacted]	-	[redacted]	[redacted]	-	[redacted]	*89,999*

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year

Note: It was not possible to obtain LY results from the cost-effectiveness model

6.4.1.1 ERG scenario analyses

A comparison of the company's scenario analyses using the ERG's preferred assumptions versus the company's base case is provided in Table 22.

Table 22: Comparison of company and ERG scenario analysis results

Scenario	ICER (£/QALY)	
	Company	**ERG**
Base-case	*30,641*	*87,920*
Company scenario analyses		
Annual discount rate (costs and outcomes) - 1.5%	*22,163*	*64,533*
Time horizon – 10 years	*62,857*	*209,605*
Time horizon – 20 years	*35,676*	*111,198*
Utility source – Li *et al.* (2017)[43]	*37,612*	*90,519*
Graft loss extrapolation – All imlifidase patients	*29,253*	*85,617*
Graft loss extrapolation – 'Unlikely to be transplanted' patients	*29,556*	*86,243*
OS with a functioning graft – 'Unlikely to be transplanted' patients	*46,896*	*187,808*
No caregiver disutility	*31,012*	*85,607*
Caregiver disutility source – Gray *et al.* (2019)[52]	*29,036*	*91,136*
ERG scenario analyses		
Account for 51/52 patients achieving a negative FACS crossmatch (proportion of imlifidase patient to receive a transplant – 94.4%)	*34,442*	*91,513*
Proportion of imlifidase patients to receive a transplant – 90%	*37,821*	*101,062*
Proportion of imlifidase patients to receive a transplant – 99%	*31,294*	*83,029*
Proportion of dialysis patients to receive a transplant – 5%	*33,727*	*54,617*
Proportion of dialysis patients to receive a transplant – 10%	*37,269*	*59,350*
Proportion of dialysis patients to receive a transplant – 20%	*45,681*	*70,678*
Use UKRR distribution of dialysis modalities	*33,771*	*85,437*
Proportion of haemodialysis patients with a caregiver – 100%	*30,641*	*88,185*
Apply HR to iBox graft estimates – 0.90	*33,605*	*93,968*
Apply HR to iBox graft estimates – 0.95	*32,036*	*90,768*
Apply alternative transplant cost - £21,000	*32,354*	*90,015*
Change comparator to 'Non-sensitised transplant'	*Dominated*	*Dominated*
Change OS dialysis source – ERA-EDTA	*33,819*	*81,137*

Key: ERA-EDTA, European Renal Association – European Dialysis Transplant Association; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life-year;

Figure 3 presents a heat map showing the effect on the company's base case ICER (without ERG correction) when the proportion of patients to receive a transplant in the intervention and

comparator arms is varied. The company's base case, 100% imlifidase patients to receive transplant, 0% comparator to receive transplant, is highlighted on the figure.

Figure 3: Heat map of the company's base case assumptions varied by the proportion to receive transplant in each arm

Proportion of dialysis patients who receive a transplant	*Proportion of imlifidase patients who receive a transplant*										
	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%
0%	31k	31k	32k	33k	33k	34k	35k	35k	36k	37k	38k
1%	31k	32k	32k	33k	34k	35k	35k	36k	37k	38k	38k
2%	32k	32k	33k	34k	35k	35k	36k	37k	38k	38k	39k
3%	32k	33k	34k	35k	35k	36k	37k	38k	38k	39k	40k
4%	33k	34k	34k	35k	36k	37k	38k	38k	39k	40k	41k
5%	34k	34k	35k	36k	37k	37k	38k	39k	40k	41k	42k
6%	34k	35k	36k	37k	37k	38k	39k	40k	41k	42k	43k
7%	35k	36k	37k	37k	38k	39k	40k	41k	42k	42k	43k
8%	36k	37k	37k	38k	39k	40k	41k	42k	42k	43k	44k
9%	37k	37k	38k	39k	40k	41k	42k	42k	43k	44k	45k
10%	37k	38k	39k	40k	41k	41k	42k	43k	44k	45k	46k
11%	38k	39k	40k	41k	41k	42k	43k	44k	45k	46k	47k
12%	39k	40k	40k	41k	42k	43k	44k	45k	46k	47k	48k
13%	40k	40k	41k	42k	43k	44k	45k	46k	47k	48k	49k
14%	40k	41k	42k	43k	44k	45k	46k	47k	48k	49k	50k
15%	41k	42k	43k	44k	45k	46k	47k	48k	49k	50k	51k
16%	42k	43k	44k	45k	46k	47k	48k	49k	50k	51k	52k
17%	43k	44k	45k	46k	47k	48k	49k	50k	51k	52k	53k
18%	44k	45k	46k	47k	48k	49k	50k	51k	52k	53k	55k
19%	45k	46k	47k	48k	49k	50k	51k	52k	53k	55k	56k
20%	46k	47k	48k	49k	50k	51k	52k	53k	55k	56k	57k
21%	47k	48k	49k	50k	51k	52k	53k	54k	56k	57k	58k
22%	48k	49k	50k	51k	52k	53k	54k	56k	57k	58k	60k
23%	49k	50k	51k	52k	53k	54k	56k	57k	58k	60k	61k
24%	50k	51k	52k	53k	54k	56k	57k	58k	60k	61k	62k
25%	51k	52k	53k	54k	56k	57k	58k	59k	61k	62k	64k
26%	52k	53k	54k	55k	57k	58k	59k	61k	62k	64k	65k
27%	53k	54k	55k	57k	58k	59k	61k	62k	64k	65k	67k
28%	54k	55k	57k	58k	59k	61k	62k	64k	65k	67k	68k
29%	55k	57k	58k	59k	61k	62k	64k	65k	67k	68k	70k
30%	56k	58k	59k	61k	62k	63k	65k	67k	68k	70k	72k
31%	58k	59k	60k	62k	63k	65k	66k	68k	70k	72k	73k
32%	59k	60k	62k	63k	65k	66k	68k	70k	71k	73k	75k
33%	60k	62k	63k	65k	66k	68k	70k	71k	73k	75k	77k
34%	62k	63k	65k	66k	68k	70k	71k	73k	75k	77k	79k
35%	63k	65k	66k	68k	70k	71k	73k	75k	77k	79k	81k

Figure 4 presents a heat map showing the effect on the company's base case ICER with ERG correction when the proportion of patients to receive a transplant in the intervention and comparator arms is varied. The company's base case, 100% imlifidase patients to receive transplant, 0% comparator to receive transplant, is highlighted on the figure.

Figure 4: Heat map of the company's ERG corrected base case assumptions varied by the proportion to receive transplant in each arm

Proportion of dialysis patients who receive a transplant	Proportion of imlifidase patients who receive a transplant										
	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%
0%	32k	32k	33k	34k	34k	35k	36k	36k	37k	38k	39k
1%	32k	33k	34k	34k	35k	36k	36k	37k	38k	39k	40k
2%	33k	34k	34k	35k	36k	36k	37k	38k	39k	40k	40k
3%	34k	34k	35k	36k	36k	37k	38k	39k	39k	40k	41k
4%	34k	35k	36k	36k	37k	38k	39k	39k	40k	41k	42k
5%	35k	36k	36k	37k	38k	39k	39k	40k	41k	42k	43k
6%	35k	36k	37k	38k	39k	39k	40k	41k	42k	43k	44k
7%	36k	37k	38k	38k	39k	40k	41k	42k	43k	44k	44k
8%	37k	38k	38k	39k	40k	41k	42k	43k	44k	44k	45k
9%	38k	38k	39k	40k	41k	42k	43k	43k	44k	45k	46k
10%	38k	39k	40k	41k	42k	43k	43k	44k	45k	46k	47k
11%	39k	40k	41k	42k	42k	43k	44k	45k	46k	47k	48k
12%	40k	41k	42k	42k	43k	44k	45k	46k	47k	48k	49k
13%	41k	42k	42k	43k	44k	45k	46k	47k	48k	49k	50k
14%	41k	42k	43k	44k	45k	46k	47k	48k	49k	50k	51k
15%	42k	43k	44k	45k	46k	47k	48k	49k	50k	51k	52k
16%	43k	44k	45k	46k	47k	48k	49k	50k	51k	52k	53k
17%	44k	45k	46k	47k	48k	49k	50k	51k	52k	53k	55k
18%	45k	46k	47k	48k	49k	50k	51k	52k	53k	54k	56k
19%	46k	47k	48k	49k	50k	51k	52k	53k	54k	56k	57k
20%	47k	48k	49k	50k	51k	52k	53k	54k	56k	57k	58k
21%	48k	49k	50k	51k	52k	53k	54k	56k	57k	58k	59k
22%	49k	50k	51k	52k	53k	54k	55k	57k	58k	59k	61k
23%	50k	51k	52k	53k	54k	55k	57k	58k	59k	61k	62k
24%	51k	52k	53k	54k	55k	57k	58k	59k	61k	62k	63k
25%	52k	53k	54k	55k	57k	58k	59k	60k	62k	63k	65k
26%	53k	54k	55k	56k	58k	59k	60k	62k	63k	65k	66k
27%	54k	55k	56k	58k	59k	60k	62k	63k	65k	66k	68k
28%	55k	56k	58k	59k	60k	62k	63k	65k	66k	68k	69k
29%	56k	58k	59k	60k	62k	63k	65k	66k	68k	69k	71k
30%	58k	59k	60k	62k	63k	64k	66k	68k	69k	71k	73k
31%	59k	60k	62k	63k	64k	66k	67k	69k	71k	72k	74k
32%	60k	61k	63k	64k	66k	67k	69k	71k	72k	74k	76k
33%	61k	63k	64k	66k	67k	69k	71k	72k	74k	76k	78k
34%	63k	64k	66k	67k	69k	71k	72k	74k	76k	78k	80k
35%	64k	66k	67k	69k	71k	72k	74k	76k	78k	80k	82k

Error! Reference source not found. 5 presents a heat map showing the effect on the ERG's base case when the proportion of patients to receive a transplant in the intervention and comparator arms is varied. The ERG's base case, 96.3% imlifidase patients to receive transplant, 31.4% comparator to receive transplant, is highlighted on the figure.

Figure 5: Heat map of the ERG's base case assumptions varied by the proportion to receive transplant in each arm

Proportion of dialysis patients who receive a transplant	Proportion of imlifidase patients who receive a transplant										
	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%
0%	47k	48k	49k	50k	51k	52k	52k	53k	54k	55k	56k
1%	48k	49k	50k	51k	51k	52k	53k	54k	55k	56k	57k
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3%	50k	50k	51k	52k	53k	54k	55k	56k	57k	58k	59k
4%	50k	51k	52k	53k	54k	55k	56k	57k	58k	59k	60k
5%	51k	52k	53k	54k	55k	56k	57k	58k	59k	60k	61k
6%	52k	53k	54k	55k	56k	57k	58k	59k	60k	61k	62k
7%	53k	54k	55k	56k	57k	58k	59k	60k	61k	62k	63k
8%	54k	55k	56k	57k	58k	59k	60k	61k	62k	63k	64k
9%	55k	56k	57k	58k	59k	60k	61k	62k	63k	64k	66k
10%	55k	57k	58k	59k	60k	61k	62k	63k	64k	65k	67k
11%	56k	57k	59k	60k	61k	62k	63k	64k	65k	67k	68k
12%	57k	58k	60k	61k	62k	63k	64k	65k	67k	68k	69k
13%	58k	59k	61k	62k	63k	64k	65k	66k	68k	69k	70k
14%	59k	60k	62k	63k	64k	65k	66k	68k	69k	70k	72k
15%	60k	61k	63k	64k	65k	66k	68k	69k	70k	72k	73k
16%	61k	63k	64k	65k	66k	67k	69k	70k	71k	73k	74k
17%	62k	64k	65k	66k	67k	69k	70k	71k	73k	74k	76k
18%	64k	65k	66k	67k	69k	70k	71k	73k	74k	76k	77k
19%	65k	66k	67k	68k	70k	71k	73k	74k	76k	77k	79k
20%	66k	67k	68k	70k	71k	72k	74k	75k	77k	79k	80k
21%	67k	68k	70k	71k	72k	74k	75k	77k	78k	80k	82k
22%	68k	70k	71k	72k	74k	75k	77k	78k	80k	82k	83k
23%	69k	71k	72k	74k	75k	77k	78k	80k	81k	83k	85k
24%	71k	72k	74k	75k	77k	78k	80k	81k	83k	85k	87k
25%	72k	73k	75k	76k	78k	80k	81k	83k	85k	87k	88k
26%	73k	75k	76k	78k	80k	81k	83k	85k	86k	88k	90k
27%	75k	76k	78k	79k	81k	83k	84k	86k	88k	90k	92k
28%	76k	78k	79k	81k	83k	84k	86k	88k	90k	92k	94k
29%	78k	79k	81k	83k	84k	86k	88k	90k	92k	94k	96k
30%	79k	81k	82k	84k	86k	88k	90k	92k	94k	96k	98k
31%	81k	82k	84k	86k	88k	90k	92k	94k	96k	98k	100k
32%	82k	84k	86k	88k	89k	91k	93k	96k	98k	100k	102k
33%	84k	86k	87k	89k	91k	93k	95k	98k	100k	102k	105k
34%	86k	87k	89k	91k	93k	95k	98k	100k	102k	104k	107k
35%	87k	89k	91k	93k	95k	97k	100k	102k	104k	107k	109k

6.5 Conclusions of the cost-effectiveness section

The work performed by the ERG addresses several shortcomings in the company submission. Although the model calculations were mostly accurate (with corrections having small influences on the ICER), the model omitted to include the appropriate application of the intervention (via an ITT approach) and the appropriate comparator. Other changes to parameters included using appropriate quality of life data, and accounting for missing costs.

Although the ERG's base case ICER increased substantially, this was almost entirely due to reflecting the decision problem, reflecting that not all imlifidase patients achieve transplant and

not all standard care patients fail to achieve transplant. For completeness, changing only these two items increased the ICER from the company's base case of £30,641 to £63,585; with correcting costing and other issues (such as utilities) accounting for the remaining increase to £87,920 which represents the ERG's base case.

The findings of sensitivity and scenario analysis further demonstrated the importance of understanding the opportunity cost of kidneys (which leads to imlifidase being dominated, a loss of [redacted] QALYs to the health care system using a £30,000 threshold and the company's uncorrected assumptions). Other important factors included the survival of patients (which the ERG was unable to adequately assess given the data used), and utility values used (which are uncertain due to being taken from the literature, and not the specific population). The remaining issue the ERG noted was the structural uncertainty present in the model. Although the company model with the ERG base case represents a reasonable estimation given the information available, there exists uncertainty in how imlifidase would be used in practice, what the survival of patients would look like, and their quality of life (as no data was captured in the clinical trial). Although not able to be included in the model, these are uncertainties that the ERG would highlight.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Imlifidase for preventing kidney transplant rejection

Date: 15 April 2021

Dear Gina and Marcus,

At the appraisal committee meeting for this topic on 11 March 2021 the appraisal committee did not recommend imlifidase. The committee agreed that further information was needed on several aspects of the company's approach before consulting on a recommendation. This letter provides a brief summary of the key issues discussed by the committee in order for you to understand its preferred assumptions and what it thought were the most plausible cost effectiveness estimates.

Currently, the appraisal committee considered that it was plausible that the incremental cost effectiveness ratio (ICER) would be at least £87,920 per QALY gained (in line with the ERG base case) for imlifidase compared with standard of care. This could greatly exceed £94,309 per QALY gained if there is any reduction in graft survival to the point where a lifetime perspective is no longer appropriate.

The committee's preferred assumptions were as follows:

- 96.3% or 94.4% used as the proportion of people who had imlifidase and had a subsequent transplant
    - To reflect the outcomes in the imlifidase trials, and reflect the realities of NHS practice where there are protocols in place to have a second person from the waiting list ready for transplant as a back-up (so a person not reaching negative crossmatch after imlifidase would not go on to have transplant).
- Li et al. (2017) or Cooper et al. (2020) used as the source of utility data
    - Li et al. is UK specific so better reflects changing clinical practice, and Cooper et al. is more recent than company's preferred source and features longitudinal estimates
- Lifetime transplant rate in the comparator arm set to 31.44%
    - Uses recent NHS Blood and Transplant data, and to reflect changes after Kidney Offering Scheme algorithm change, prioritising people who are more highly sensitised

The £94,309 per QALY gained figure was the result of using 31.44% for the rate of transplant in comparator arm, Li et al. as the utility source, and 94.4% of people having a transplant after imlifidase.

The clinical experts at the meeting stated that the appropriate population who may be considered for imlifidase in the NHS would have a calculated reaction frequency of at least 99%. Some clinical experts at the meeting suggested that a suitable population could be people who:

- cannot have a transplant even after all possible delisting strategies had been used, and
- could tolerate a transplant with a non-perfect match, and
- have been on the waiting list for a year or more (so there would be a chance for the allocation algorithm to find them a match that has a negative crossmatch without using imlifidase first).

When asked about how a possible recommendation might be implemented, and who might be considered for imlifidase, the commissioning expert at the meeting explained that a national multidisciplinary team would be needed to develop the pathways and protocol for imlifidase. They suggested that treatment could potentially be focused in around 4 specialist centres across the country. The committee concluded the treatment pathway and target population in the NHS was still unknown. This means that Hansa Biopharma, with involvement from clinicians and commissioners, need to identify and define the population who would most benefit from imlifidase, as well as confirm the treatment pathway. This could potentially have the greatest impact on the cost-effectiveness estimates.

To request a surgery with NHS England and NHS Improvement (NHSE/I) clinical and commissioning colleagues please email england.commercialmedicines@nhs.net with a short summary of the issue outlined here and indicate the type of expertise required of NHSE/I colleagues to ensure the right mix of attendees.

Additionally, given the clinical uncertainties in the evidence, you may wish to explore opportunities for further data collection and monitoring with NICE's managed access team, and consider making a proposal for a recommendation for managed access ahead of the next committee meeting. To aid you in discussions about managed access data collection we have outlined the other main areas of uncertainty which are likely to impact cost-effectiveness below. To arrange a meeting with the NICE managed access team, please email your request with some dates and times reflecting your availability to: ManagedAccessTeam@nice.nhs.uk.

We would be grateful to understand how you intend to address the issues outlined in this letter by 7 May 2021, so that we can plan for the next steps in this technology appraisal.

Yours sincerely,

Jasdeep Hayre, Associate Director, Technology Appraisals & HST

Long term outcomes with imlifidase

- Although there is an ongoing follow-up study, the clinical experts stated that the trial outcomes so far are too short for this clinical context (with potential graft loss at 5, 10 and 15 years). Data on long-term outcomes would be critical for deciding whether imlifidase should be recommended in the NHS:

Long-term graft survival and iBox model

- A scenario analysis showed that any reduction in graft survival would have a major effect on the cost effectiveness of imlifidase. Over longer time horizons, graft survival could be quite different between a general transplant population and the highly sensitised target population, so it may not be appropriate to use the predictions from iBox (developed based on a general transplant population). The committee considered that it would be too optimistic to expect such similar graft survival prospects from the iBox projection and the extrapolation of the trial data using Weibull, especially at 20 years.
- The ERG was concerned about the difference in the proportion of people with a previous transplant between the population in this appraisal and the iBox population to whom data was fitted (60% and 15%, respectively). There may be selection biases, and predictions from this model may not be generalisable to the target population. So graft survival data collected specifically within an agreed target population in the NHS would be informative for decision making.
- If graft survival after imlifidase in clinical practice for people who are highly sensitised is worse than the modelled extrapolation of graft survival from the trial, then more people than modelled would start dialysis more quickly after transplant. This would mean there would be no further dialysis cost savings for them, and the ICER would increase. Graft survival could be related to how well immunosuppressant regimens are adhered to, which is not captured by iBox.
- To aid decision-making, longer-term graft survival data from imlifidase trials could be presented, as well as real-world (NHS) graft survival data. This would allow for consideration of NHS-specific graft survival outcomes, as well as seeing how extrapolations and the iBox prediction are affected, and whether predictions are improved.

Antibody-mediated rejection

- The committee noted the high rate of antibody-mediated rejection (40%) in the company-defined target population. There was no comparator arm in the trials nor matched population (and lack of clarity on what that population should be). It was not clear whether the 40% antibody-mediated rejection (AMR) was a consequence of a very severe population in the imlifidase trials, or if antibody-mediated rejection was unusually high in the trials. Clinical experts explained that in clinical practice they would normally expect only 10% of people to have antibody-mediated rejection after an incompatible transplant, based on UK experience. To address some of these uncertainties, data could be collected on:
    - Proportion of people with acute and chronic AMR after imlifidase;
    - Proportion with signs of AMR on biopsy (checked at regular intervals) after imlifidase;
    - How AMR after imlifidase gets treated in the NHS (treatments used, duration of treatments, costs, resource use);
    - Outcomes after AMR such as return to dialysis or subsequent transplant.

Treatment pathway for people having imlifidase

- If imlifidase were to be recommended for managed access, data collection could include the following about prior and subsequent treatment, as they could have an impact on long-term outcomes after imlifidase:
    - If patients had dialysis, and if so, how long for;
    - Whether patients had a previous kidney transplant, and if so, how many;
    - Outcomes after imlifidase such as return to dialysis or subsequent transplant.

Other areas of uncertainty after ACM1

Higher intensity immunosuppression regimens

- The company's model did not differentiate between a graft needing intensive immunosuppression therapy and one which was more successful. Acquisition costs and adverse event costs of the higher intensity immunosuppression regimens used by some people in the imlifidase trials after transplant were not modelled for the NHS population, and drugs within these regimens are not currently commissioned in the NHS. To address these uncertainties, data could be collected on:
    - How many patients need more intensive immunosuppression after imlifidase;

- Which drugs are used for more intensive immunosuppression regimens in the NHS, with associated costs and outcomes.

Utilities

- As utility values were not collected in the imlifidase trials, data could be collected on utility values for participants, preferably EQ-5D, both before and after imlifidase, and at various stages of follow-up. This would allow the committee to consider NHS-specific utility values, with possible support from/comparison with published sources. In particular, the effects of AMR (both acute and chronic) and more intensive immunosuppression regimens on utility scores would be useful to capture, as the committee had concerns over these areas.

Ways of presenting the clinical-effectiveness data that would allow full validation

- The ERG highlighted that Hansa Biopharma could have provided the clinical-effectiveness data in a way that would have given greater confidence in the findings. The committee acknowledged that Hansa Biopharma had provided all the data it had available at that point but agreed with the ERG that the data could have been presented in a more meaningful way to allow for validation. Therefore, the following would help allow full validation of the clinical-effectiveness estimates:
    - Rates of crossmatch conversion, specifying the test and length of follow up. Ideally, separate rates for each type of test individually, because of known variation in the sensitivity or specificity. Length of follow up with variance should also be reported, and it would be useful to have rates reported at timepoints that would be informative to conceptualise the treatment pathway for imlifidase (for example 2 hours, 4 hours, 6 hours, 8 hours and so on).
    - Mean or median change (both if possible) in mean fluorescence intensity levels specific to donor-specific antibodies accompanied by variance data.
    - Rate of transplant rejection, rate of acute and chronic antibody-mediated rejection, number of cases of antibody-mediated rejection resolved by 6 months, number of cases of antibody-mediated rejection that resulted in graft loss.
    - Time to event data for the rebound of donor-specific antibodies after transplant, and variance around the rise in mean fluorescence intensity levels reported at timepoints in the company submission (day 7 to day 30).
    - Proportion needing treatment for the rebound of antibodies after transplant at multiple timepoints which would inform decision making (for example, 48

hours, 1 week, 1 month, 6 months), and the nature and timepoint of treatment.

- Rate of infection (overall and treatment-related) because it would be useful to see how many of the those who had a second dose exhibited an infection.

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May 7th, 2021

Jasdeep Hayre, Associate Director
Technology Appraisals & HST

Dear Jasdeep,

Thank you for your letter dated 15th April 2021 (see Appendix A). As requested, please find below Hansa Biopharma's proposed actions to address the issues outlined in the Appraisal Committee's feedback. This will in turn allow for planning the next steps of the technology appraisal for imlifidase.

Hansa and the NICE Managed Access Team (MAT) also met on 28th April 2021 to review the uncertainties raised following the Appraisal Committee Meeting and agreed that calculated reaction frequency (cRF) and time on dialysis are key criteria that will help ensure that imlifidase targets highly sensitized patients who are unlikely to be transplanted, but also gives the Kidney Offering Scheme an opportunity to work.

Firstly, Hansa is seeking to gain access to data from the NHS Blood and Transplant (NHSBT) database. The NHSBT collates patient-level data on kidney transplant recipients as well as those on the waiting list for a kidney transplant. Analysis of this data will help Hansa and commissioners gain a better understanding of which patients have been transplanted under the Kidney Offering Scheme, and when a patient becomes unlikely to be transplanted. As a result, this will support Hansa in defining the positioning of imlifidase in the current treatment pathway and determining the potential impact of imlifidase on the Kidney Offering Scheme. This data analysis will also support NHSBT's aim to provide fair and equitable allocation of deceased donor kidneys by identifying the highly sensitised patients who remain unlikely to receive a transplant, despite the significant success of the Kidney Offering Scheme. The NICE MAT team has agreed to work with Hansa to facilitate data access from the NHSBT database. Hansa will share NHSBT contacts and the relevant requests to gain access to NHSBT data available for cRF=99% and cRF=100% patients.

In parallel to analysing NHSBT data, Hansa will engage with clinicians and commissioners to identify and define the population that would most benefit from imlifidase and confirm the positioning in the treatment pathway. Hansa are reaching out to clinical experts to reach consensus opinion on eligibility/ineligibility criteria for imlifidase use, specifically focusing on cRF and time on dialysis. Requiring time on dialysis -to determine the suitable imlifidase patient population is an important element to allow the Kidney Offering Scheme a chance to work, and will address the ERG's assumption that some patients in the Standard of Care arm may not yet be on dialysis. We will also develop a proposed treatment pathway with these clinicians. Hansa will then undertake further analysis of the clinical data. This will allow us to clarify the uncertainties raised in relation to the committee's preferred assumptions.

Hansa will continue to work with the NICE MAT team to evaluate the feasibility of using our post-licensing study and validation of the iBOX-modelled long-term outcomes to address clinical uncertainties.

Hansa have also requested support from NICE MAT in getting access to the Getting It Right First Time (GIRFT) National Report on Renal Medicine. Our recent email correspondence on March 22, 2021 with Michelle Carter, Communications and Media Relations Manager, indicated that the national report for renal medicine is complete in draft form but is awaiting formal approval. Hansa believe the report will provide the latest and most comprehensive understanding of the full cost of dialysis in the UK.

Hansa will liaise with NHS England and NHS Improvement (NHSE/I) clinical and commissioning colleagues, to discuss commercial and clinical issues and gain support in further developing a national multidisciplinary team framework to develop the pathways and protocol for imlifidase.

Hansa has discussed with the NICE MAT the suitability of a Managed Access Agreement to develop a Data Collection Agreement, as defined by the NICE appraisal committee, to mitigate the clinical uncertainty of imlifidase. In parallel, either a Commercial Access Agreement or a Patient Access Scheme will be implemented to offer imlifidase at a cost-effective price for the duration of the MAA, if an MAA is agreed to be the appropriate route.

Throughout this process Hansa will coordinate with the Patient Access Scheme Liaison Unit (PASLU) and we will keep the NICE MAT informed of progress.

We would be grateful for your feedback on the above proposal, and we would welcome the opportunity to discuss our proposal further. We are keen to progress these elements promptly and we would like to be able to update you on a regular basis. Please advise on the best way to do this.

Sincerely

Stuart Mudunkotuwe
European Market Access Lead
Hansa Biopharma
Stuart.mundunkotuwe@hansabiopharma.com

Elodie Denjean
Commercial Territory Manager
Hansa Biopharma
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Appendix A

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Imlifidase for preventing kidney transplant rejection

Date: 15 April 2021

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The committee's preferred assumptions were as follows:

- 96.3% or 94.4% used as the proportion of people who had imlifidase and had a subsequent transplant
    - To reflect the outcomes in the imlifidase trials, and reflect the realities of NHS practice where there are protocols in place to have a second person from the waiting list ready for transplant as a back-up (so a person not reaching negative crossmatch after imlifidase would not go on to have transplant).
- Li et al. (2017) or Cooper et al. (2020) used as the source of utility data
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- have been on the waiting list for a year or more (so there would be a chance for the allocation algorithm to find them a match that has a negative crossmatch without using imlifidase first).

When asked about how a possible recommendation might be implemented, and who might be considered for imlifidase, the commissioning expert at the meeting explained that a national multidisciplinary team would be needed to develop the pathways and protocol for imlifidase. They suggested that treatment could potentially be focused in around 4 specialist centres across the country. The committee concluded the treatment pathway and target population in the NHS was still unknown. This means that Hansa Biopharma, with involvement from clinicians and commissioners, need to identify and define the population who would most benefit from imlifidase, as well as confirm the treatment pathway. This could potentially have the greatest impact on the cost-effectiveness estimates.

To request a surgery with NHS England and NHS Improvement (NHSE/I) clinical and commissioning colleagues please email england.commercialmedicines@nhs.net with a short summary of the issue outlined here and indicate the type of expertise required of NHSE/I colleagues to ensure the right mix of attendees.

Additionally, given the clinical uncertainties in the evidence, you may wish to explore opportunities for further data collection and monitoring with NICE's managed access team, and consider making a proposal for a recommendation for managed access ahead of the next committee meeting. To aid you in discussions about managed access data collection we have outlined the other main areas of uncertainty which are likely to impact cost-effectiveness below. To arrange a meeting with the NICE managed access team, please email your request with some dates and times reflecting your availability to: ManagedAccessTeam@nice.nhs.uk.

We would be grateful to understand how you intend to address the issues outlined in this letter by 7 May 2021, so that we can plan for the next steps in this technology appraisal.

Yours sincerely,

Jasdeep Hayre, Associate Director, Technology Appraisals & HST

Long term outcomes with imlifidase

- Although there is an ongoing follow-up study, the clinical experts stated that the trial outcomes so far are too short for this clinical context (with potential graft loss at 5, 10 and 15 years). Data on long-term outcomes would be critical for deciding whether imlifidase should be recommended in the NHS:

Long-term graft survival and iBox model

- A scenario analysis showed that any reduction in graft survival would have a major effect on the cost effectiveness of imlifidase. Over longer time horizons, graft survival could be quite different between a general transplant population and the highly sensitised target population, so it may not be appropriate to use the predictions from iBox (developed based on a general transplant population). The committee considered that it would be too optimistic to expect such similar graft survival prospects from the iBox projection and the extrapolation of the trial data using Weibull, especially at 20 years.
- The ERG was concerned about the difference in the proportion of people with a previous transplant between the population in this appraisal and the iBox population to whom data was fitted (60% and 15%, respectively). There may be selection biases, and predictions from this model may not be generalisable to the target population. So graft survival data collected specifically within an agreed target population in the NHS would be informative for decision making.
- If graft survival after imlifidase in clinical practice for people who are highly sensitised is worse than the modelled extrapolation of graft survival from the trial, then more people than modelled would start dialysis more quickly after transplant. This would mean there would be no further dialysis cost savings for them, and the ICER would increase. Graft survival could be related to how well immunosuppressant regimens are adhered to, which is not captured by iBox.
- To aid decision-making, longer-term graft survival data from imlifidase trials could be presented, as well as real-world (NHS) graft survival data. This would allow for consideration of NHS-specific graft survival outcomes, as well as seeing how extrapolations and the iBox prediction are affected, and whether predictions are improved.

Antibody-mediated rejection

- The committee noted the high rate of antibody-mediated rejection (40%) in the company-defined target population. There was no comparator arm in the trials nor

matched population (and lack of clarity on what that population should be). It was not clear whether the 40% antibody-mediated rejection (AMR) was a consequence of a very severe population in the imlifidase trials, or if antibody-mediated rejection was unusually high in the trials. Clinical experts explained that in clinical practice they would normally expect only 10% of people to have antibody-mediated rejection after an incompatible transplant, based on UK experience. To address some of these uncertainties, data could be collected on:

- Proportion of people with acute and chronic AMR after imlifidase;
- Proportion with signs of AMR on biopsy (checked at regular intervals) after imlifidase;
- How AMR after imlifidase gets treated in the NHS (treatments used, duration of treatments, costs, resource use);
- Outcomes after AMR such as return to dialysis or subsequent transplant.

Treatment pathway for people having imlifidase

- If imlifidase were to be recommended for managed access, data collection could include the following about prior and subsequent treatment, as they could have an impact on long-term outcomes after imlifidase:
  - If patients had dialysis, and if so, how long for;
  - Whether patients had a previous kidney transplant, and if so, how many;
  - Outcomes after imlifidase such as return to dialysis or subsequent transplant.

Other areas of uncertainty after ACM1

Higher intensity immunosuppression regimens

- The company's model did not differentiate between a graft needing intensive immunosuppression therapy and one which was more successful. Acquisition costs and adverse event costs of the higher intensity immunosuppression regimens used by some people in the imlifidase trials after transplant were not modelled for the NHS population, and drugs within these regimens are not currently commissioned in the NHS. To address these uncertainties, data could be collected on:
  - How many patients need more intensive immunosuppression after imlifidase;
  - Which drugs are used for more intensive immunosuppression regimens in the NHS, with associated costs and outcomes.

Utilities

- As utility values were not collected in the imlifidase trials, data could be collected on utility values for participants, preferably EQ-5D, both before and after imlifidase, and

at various stages of follow-up. This would allow the committee to consider NHS-specific utility values, with possible support from/comparison with published sources. In particular, the effects of AMR (both acute and chronic) and more intensive immunosuppression regimens on utility scores would be useful to capture, as the committee had concerns over these areas.

Ways of presenting the clinical-effectiveness data that would allow full validation

- The ERG highlighted that Hansa Biopharma could have provided the clinical-effectiveness data in a way that would have given greater confidence in the findings. The committee acknowledged that Hansa Biopharma had provided all the data it had available at that point but agreed with the ERG that the data could have been presented in a more meaningful way to allow for validation. Therefore, the following would help allow full validation of the clinical-effectiveness estimates:
    - Rates of crossmatch conversion, specifying the test and length of follow up. Ideally, separate rates for each type of test individually, because of known variation in the sensitivity or specificity. Length of follow up with variance should also be reported, and it would be useful to have rates reported at timepoints that would be informative to conceptualise the treatment pathway for imlifidase (for example 2 hours, 4 hours, 6 hours, 8 hours and so on).
    - Mean or median change (both if possible) in mean fluorescence intensity levels specific to donor-specific antibodies accompanied by variance data.
    - Rate of transplant rejection, rate of acute and chronic antibody-mediated rejection, number of cases of antibody-mediated rejection resolved by 6 months, number of cases of antibody-mediated rejection that resulted in graft loss.
    - Time to event data for the rebound of donor-specific antibodies after transplant, and variance around the rise in mean fluorescence intensity levels reported at timepoints in the company submission (day 7 to day 30).
    - Proportion needing treatment for the rebound of antibodies after transplant at multiple timepoints which would inform decision making (for example, 48 hours, 1 week, 1 month, 6 months), and the nature and timepoint of treatment.
    - Rate of infection (overall and treatment-related) because it would be useful to see how many of the those who had a second dose exhibited an infection.

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8th October 2021

Jasdeep Hayre, Associate Director
Technology Appraisals & HST

Brad Groves, Associate Director,
Managed Access

Dear Jasdeep and Brad,

Hansa Biopharma, would like to provide an update on the significant progress made in addressing the uncertainties raised for the technology appraisal: *imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]*, with the aim of resuming the appraisal process as efficiently as possible to ensure imlifidase is made available to appropriate patients in a timely manner.

Following this first appraisal committee meeting on 11th March 2021, NICE paused the appraisal process and summarised the uncertainties to Hansa in a letter dated 15th April 2021. In this letter NICE recommended that Hansa engage further with NICE and NHSE&I and a clinical and commercial surgery meeting was held on the 12th August 2021. Taking into account the advice received during the surgery meeting as well as further productive and collaborative engagement across the health system in England, this letter demonstrates how Hansa has addressed the uncertainties raised by NICE:

Summary

1. **Eligible patient population**

Hansa has updated the imlifidase eligible patient population proposed by NICE to more restrictive criteria, reflecting data provided NHS Blood and Transplant (NHSBT) and clinical expert feedback, to help identify the highly sensitised patient population who are unlikely to be transplanted:

- Eligibility Criteria

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- cRF≥99%, and
- Matchability Score = 10, and
- Waiting time ≥ 2 years

- Clinical Considerations
  - All possible delisting strategies explored
  - Patient is medically fit to receive a transplant with increased immunological risk
  - And patient understands and is willing to consider an increased immunological risk transplant

2. Care pathway and national multidisciplinary team (MDT)

- Hansa has outlined how imlifidase can be routinely incorporated into the current care pathway utilising clinical expert opinion and the CRG renal services specification for Adult Kidney Transplantation Service.
- Hansa is open to the development of a national MDT and we look forward to working with NICE and NHSE&I in alignment with the appraisal recommendation.

3. Long term efficacy and safety

- Hansa has presented the imlifidase trial data in a more meaningful way, as suggested by the ERG, to help validate the clinical effectiveness estimates.
- Since the appraisal committee meeting, data on outcomes up–to 3 years post-transplant in imlifidase-desensitised kidney transplant patients has been published. This data concluded that outcomes for patients receiving an imlifidase-enabled kidney transplant resembled those in other highly sensitised patients who have undergone renal transplantation at 3 years post transplantation
- A Post-Authorisation Efficacy and Safety (PAES) study will be conducted to further validate the clinical effectiveness and safety profile of imlifidase.

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4. **Cost-effectiveness model**
    - Hansa questions four assumptions within the ERG cost effectiveness model design. Removing these assumptions results in the ERG's base case model ICER changing from £[redacted] to £[redacted] per QALY.
    - Hansa has revised its base case model assumptions, based on the NHSBT data for the proposed imlifidase patient population, the updated 3-year post-transplant data, ERG's concerns regarding the iBox graft loss extrapolations, and other ERG preferred assumptions.

5. **Revised Base Case**
    - Based on the revised base case cost effectiveness scenario, taking into account NHSE&I/NICE feedback, NHSBT data on the eligible patient population and ERG preferred model assumptions, Hansa wish to propose a revised simple PAS discount totalling [redacted] which will demonstrate that imlifidase is a cost-effective treatment for patients in England

We look forward to working with NICE to resume the appraisal process as efficiently as possible to ensure imlifidase is made available to appropriate patients in a timely manner.

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1. Eligible patient population

1.1. Uncertainties raised and actions undertaken by Hansa to address them

NICE emphasised the need to specifically define the patient population eligible for imlifidase in order to ensure that imlifidase is only used for those highly sensitised patients who are unlikely to receive a transplant under the UK Kidney Offering Scheme (KOS). In your letter dated 15th April 2021, NICE suggested the following definition of the patient population eligible for treatment with imlifidase:

calculated reaction frequency of at least 99% (cRF≥99%)

During the appraisal meeting, some of the clinical experts present suggested that a suitable population could be patients who:

- *cannot have a transplant even after all possible delisting strategies have been used, and*
- *could tolerate a transplant with a non-perfect match, and*
- *have been on the waiting list for a year or more.*

1.2. Proposed Eligible Patient Population

Hansa engaged with the NHSBT in order to gain a better understanding of transplant rates for highly sensitised patients, since the implementation of the newly revised KOS. The data collected can be found in appendix 7.1 and was presented during the NHSE&I surgery on 12th August 2021. Subsequently, Hansa engaged with the following clinical experts: Professor David Briggs, Head of Histocompatibility and Immunogenetics (H&I) laboratory, Queen Elizabeth Hospital Birmingham; Dr Sian Griffin, Consultant Nephrologist, University Hospital of Wales, and Senior Lecturer, Cardiff University; Professor Nithya Krishnan, Consultant Transplant Nephrologist, University Hospitals Coventry & Warwickshire NHS Trust; Dr Rommel Ravanan, Consultant nephrologist/Transplant Physician at North Bristol NHS Trust; and Dr Adnan Sharif, Consultant Nephrologist and Renal Transplant Physician, Birmingham; to seek their expert opinion based on the data received from NHSBT and the 7.1proposed eligible patient population.

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Based on the new data from NHSBT and on clinical expert input, Hansa proposes to define the more restricted eligible patient population as detailed in Figure 1 which was also presented at the NHSE&I surgery slot. The red text highlights variation from the NICE proposal in your letter dated 15th April 2021.

Figure 1 Proposed eligible population for imlifidase

Eligibility criteria	• cRF ≥ 99% • and Matchability Score = 10 • and been on the waiting list for 2 yrs or more (to allow for allocation algorithm to find them a match that has a negative crossmatch without using imlifidase first)
Clinical considerations	• All possible delisting strategies explored • Patient is medically fit to receive a transplant with increased immunological risk • And patient understands and is willing to consider an increased immunological risk transplant
Multidisciplinary team (MDT)	• These patients would then be assessed by a national multidisciplinary team (MDT) • The MDT should develop auditable criteria to ensure that imlifidase is allocated to patients who would otherwise be unlikely to receive a transplant

Included in the criterion is that the patient should be on the transplant waiting list for at least two years to allow the time for the kidney offering scheme to find a suitable organ without the requirement for imlifidase, and longer than the median waiting time for all adult UK kidney transplantation patients of 633 days. Moreover, a Matchability Score of 10 is one of the criteria for prioritisation of a patients in Tier A and it is estimated that the proportion of patients in Tier A and on the waiting list for ≥ 2 years who are not on dialysis is very small or zero. In our modified base case, we have therefore set this as zero percent.

Hansa therefore proposes this eligible patient population (Figure 1) to NICE and have adapted the cost-effectiveness model accordingly.

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2. Care pathway and national multidisciplinary team (MDT)

2.1. Uncertainties raised and actions undertaken by Hansa to address them

NICE commented that the treatment pathway for patients transplanted with imlifidase is still unknown. Separately, when discussing how a possible recommendation might be implemented, and which patients might be considered for transplantation with imlifidase, the commissioning expert at the meeting suggested that a national MDT may be needed to ensure consistent national use of imlifidase in line with NICE's recommendations.

Hansa engaged with clinical experts to review the CRG's renal service specifications, Renal Assessment (Adult) and Adult Kidney Transplant service (1, 2) and discussed how imlifidase could be integrated into the current care pathway.

2.2. Proposed care pathway

A draft overview of a modified care pathway is depicted in

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Figure 2. This was shared during the NHSE&I surgery on 12th August. A more detailed version of the care pathway with imlifidase was also developed and was shared with Ian Wren (NHSE&I National Programme of Care Manager). Both documents provide an accurate assessment of the anticipated impact of imlifidase on the current care pathway. The detailed version of the care pathway can be found as an additional document Annex 1: patient care pathway.

In

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Figure 2, the current care pathway is represented in the light purple boxes. The dark purple boxes outline where the current care pathway will require additional steps for imlifidase-enabled transplants.

In addition to the care pathway, Hansa would like to address the following points, which were raised during the appraisal process:

- The clinical experts consulted felt that the proposed pathway would allow imlifidase-enabled transplants to be conducted within an acceptable cold ischaemia time (CIT). It is well recognised that CIT should be minimised, and the clinicians consulted indicated that they did not anticipate an untoward increase in this time with the inclusion of imlifidase in the pathway.

- In terms of immunosuppression regimens potentially required, input gathered from clinicians in the UK clinical advisory board meeting (virtual) on 7th April 2021 suggests that the standard of care for an imlifidase-enabled transplant will be equivalent to that required for HLA incompatible transplants, which are already carried out in centres of excellence in the UK (3).

- The NICE committee concluded that the treatment pathway was unknown and that Hansa, with the involvement of clinicians and commissioners, need to identify who would most benefit from imlifidase. Hansa engaged with the clinicians named above to develop the proposed integration of imlifidase into the care pathway, shown in

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- Figure 2 with a detailed version in Annex 1. The feedback received from NHSE&I during the surgery meeting suggests that a national MDT may not be required in light of clinicians' knowledge and understanding of the use of imlifidase. Hansa is open to the development of a national MDT, and we look forward to working with NICE and NHSE&I in alignment with the appraisal recommendation.

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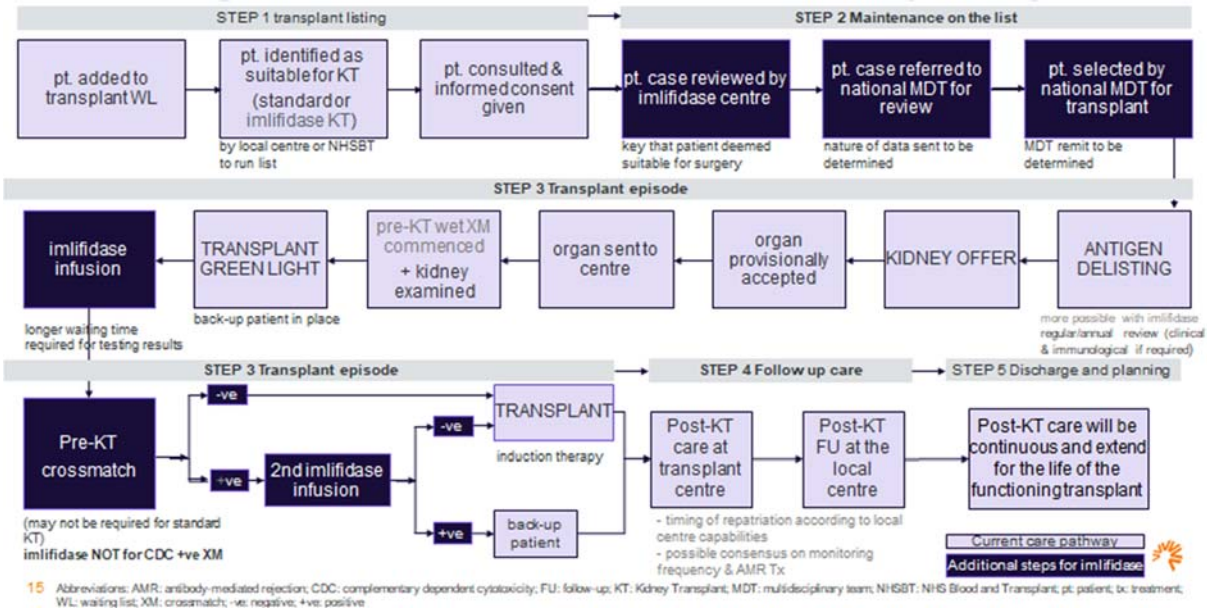
Figure 2 The proposed integration of imlifidase into the current care pathway



Abbreviations: AMR: antibody-mediated rejection; CDC: complement dependent cytotoxicity; FU: follow-up; KT: Kidney Transplant; MDT: multidisciplinary team; NHSBT: NHS Blood and Transplant; pt: patient; tx: treatment; WL: waiting list; XM: crossmatch; -ve: negative; +ve: positive

In summary, Hansa believes that the externally validated work on the care pathway adequately sets out how imlifidase could be routinely integrated into the care pathway with minimal change, and without increasing CIT.

3. Long-term efficacy and safety of imlifidase

3.1. Uncertainties raised

NICE, like the ERG, raised uncertainties about the clinical efficacy and safety data in terms of their structure and presentation, while acknowledging that Hansa had provided all the data it had available at that point. These included crossmatch conversion rates, MFI mean and median changes, rates of transplant rejection, time to event data on rebound DSA after transplant, proportion of patients needing treatment for rebound of antibodies and rates of infection. Hansa has summarised actions taken in section 3.2 with more detail available in appendix 7.3.

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NICE also noted that additional data collection could help address the uncertainties raised on antibody mediated rejection (AMR). NICE noted the clinical expert opinion that around 10% of people will experience AMR after an incompatible transplant. NICE was not clear whether the 38% incidence of AMR following an imlifidase-enabled transplant was a consequence of a very severe population in the imlifidase trials, or whether antibody-mediated rejection was unusually high in the trials. The 3-year follow-up data, published since our last interaction, has provided more clarification regarding this, see section 0.

NICE also raised concern around the duration of the long-term follow-up data available given the clinical context and concerns regarding the predictions from iBOX for graft survival being too optimistic and the potential impact that this may have on the cost effectiveness. Hansa has provided further clarification in section 3.5.

3.2. Data presentation

Hansa has generated the imlifidase trial data tables, revising the presentation of the data in the original submission, as advised by NICE and the ERG, where possible. Firstly, regarding the crossmatch conversion rate, the clinical studies were not designed to capture the time to crossmatch conversion, however data was collected following a crossmatch testing schedule as seen in
Table 3. Secondly, data was not collected to capture whether treatment for graft rejection was related to “rebound of antibodies”, however, high DSA was not treated unless clinical signs of rejection were present. Therefore, the best available data is the “graft rejection treatment” (regardless of biopsy status), which includes all suspected AMR (and therefore potentially treated to reduce DSA) and confirmed AMR, but it also includes treatment for cell-mediated rejection (CMR), see Table 11. Lastly, the time to event data for the rebound of donor-specific antibodies after transplant was visually approximated from graphs of individual patients DSAs (presented in Table 10) due to the lack of data points collected.

The remaining data presentation topics were addressed as advised. The mean and median change in MFI have been provided from pre-dose to 3 years post-dose, for all patients in Table 4, then specifically for cRF ≥99% patients in Table 5 and cRF=100% in Table 6. The rate of

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transplant rejection, rate of acute and chronic antibody-mediated rejection, number of cases of antibody-mediated rejection resolved by 6 months, and number of cases of antibody-mediated rejection that resulted in graft loss are presented in Table 7 for all patients, Table 8 in those with cRF≥99% and Table 9 in those with cRF=100%. And lastly, there are details on the rate of infection (overall and treatment-related) to see how many patients who received a second dose exhibited an infection in the SmPC (4). No difference was seen in the transplanted patients who received a 2nd dose of 0.25mg/kg (data limited to 3 patients) and those receiving one dose.

Further details are provided in appendix 7.3.

3.3. Published 3-year follow-up data

Since the appraisal committee meeting, an update to the 2-year follow up analyses originally submitted was published. In imlifidase clinical trials, 46 adult patients received imlifidase prior to transplantation with deceased- or living-donor kidney transplants. Of these, 39 were initially crossmatch positive against their donors. A recent publication describes the outcomes of the crossmatch positive cohort at 3 years post-transplant (5).

The data were additionally analysed as subgroups based on whether or not patients had experienced antibody mediated rejection (AMR+ group) or not (AMR- group) as well as the unlikely to be transplanted based on US based criteria (crossmatch positive (XM+), receipt of deceased donor, and cPRA ≥ 99.9%. The results are summarised in Table 1.

Table 1 The number of AMR positive and AMR negative patients and relative outcomes

	AMR+	AMR-
Number	15	24
Death-Censored Allograft Survival	93%	77%
Patient Survival (years)	85%	94%
eGFR (ml/min/1.73m^2)	49	61

Adapted from Kjellman et al. 2021 (5)

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The overall incidence of AMR was 38%, with the majority of these episodes taking place in the first month following transplantation. Kjellman et al noted that the onset of AMR continues to be a concern throughout the post-transplant course in highly sensitized patients. Moreover it is indicated that for patients receiving transplants following imlifidase treatment, the frequency and severity of early AMR was not substantially different from what is expected and reported in highly sensitized patients receiving incompatible kidneys (5).

As a therapy option for end stage renal disease, transplantation confers numerous advantages over dialysis which are associated with viable allograft function. In turn, compromised renal function, as indicated by reduced eGFR, negates these improvements. It is noteworthy that for the majority of patients described, the eGFR remains stable up to 3 years. This is consistent with a low probability of impending graft failure and augurs well for longer term patient and graft survival.

Kjellman et al noted that for those patients who require a kidney transplantation but have pre-formed donor-specific antibodies, there are numerous obstacles. In addition to often experiencing a long wait for a suitable kidney, there is subsequently an increased likelihood of antibody-mediated rejection post-transplant. A further consideration for these sensitized patients is that the extended time spent on dialysis is associated with greater frailty and/or comorbidity. The increased risk of infection, malignancy and cardiovascular events, themselves leads to the requirement for additional therapy.

Kjellman et al concluded that the outcomes up to 3 years of patients receiving an imlifidase-enabled kidney transplant resembled those in other highly sensitised patients who have undergone renal transplantation. The incidence of antibody-mediated injury was in line with other forms of desensitisation and considered to be manageable in this high-risk population. Furthermore, the relative stability of allograft function and long-term safety profile did not indicate any increase in the rates of infection or of malignancy. Overall, imlifidase was considered to be a potent option to enable transplantation in patients for whom dialysis is the only alternative.

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The PAES study for imlifidase is also designed to generate data to identify the incidence and impact of AMR on clinical outcomes. More detail on PAES is provided in section 0 below.

3.4. Post-Authorisation Efficacy and Safety Study (PAES)

Hansa will be conducting a phase III controlled, non-randomised, open-label post-authorisation efficacy and safety (PAES) study. This study is designed to provide comprehensive efficacy and safety data to support a future full marketing authorisation of imlifidase (Idefirix®) in the EU and the UK. The patients to be included are highly sensitised with the highest unmet medical need, unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients. This will include patients with a positive crossmatch against an available deceased donor. Fifty patients will be desensitised with imlifidase to convert a positive crossmatch to negative and then transplanted. There will be 15 to 20 trial sites in Europe, including 2 to 3 clinical sites in the UK (6).

The primary endpoint of this study is [redacted]. As mentioned above the PAES will also collect data on AMR: where a secondary endpoint is the [redacted]. The PAES will also aim to evaluate [redacted] specifically patients' life participation, as a secondary endpoint, in people that receive an imlifidase transplant, and in the non-comparative concurrent reference cohort (6). The full list of endpoints in the PAES study can be seen in appendix 7.4. These endpoints are also available on NICE Docs.

3.5. iBox tool

The recent publication of 3-year follow-up data is consistent with the previously submitted efficacy data for imlifidase and provides further confidence in the predicted graft survival rates, and the assumptions utilised in the cost-effectiveness model. This new 3-year follow-up data shows graft survival rates higher than the iBox prediction at 3 years. This suggests that iBox would be a conservative prediction of graft survival in comparison to the current imlifidase trial data available. Moreover, the predictions from the extrapolated graft survival from the trials, as can be seen in appendix 7.2, are supported by the recent publication of

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the follow-up 3-year data. However, based on NICE's concerns on iBox and given the longer length of follow-up in the trials that is now available, Hansa will therefore use the newly

published 3-year follow up data for the graft loss extrapolation within the Hansa base case cost effectiveness model, instead of iBox extrapolations.

4. Cost effectiveness modelling

Hansa has reviewed the ERG model and preferred assumptions and have detailed issues below, section 4.1; adaptations following NHSBT data analyses, section 4.2; and adaptations to the model after addressing NICE and ERG uncertainties, section 4.3.

4.1. ERG's model validation

Firstly, there were four issues identified with the implementation of the ERG's preferred assumptions in the ERG's model:

4.1.1. Calculation of the cost of haemodialysis in the ERG's model

Hansa identified inconsistencies in the calculation of the cost of haemodialysis (HD) when the patients "not on dialysis" are included. The cost of HD is calculated using a weighted average of the cost of the following three types of renal replacement therapy: hospital HD, satellite HD and home HD. When the "not on dialysis" patients are included in the model, the distribution of HD patients across these three types is 42.9%, 27.5% and 4.2% which sums up to 74.5% and not 100%. The HD cost based on this weighted average is therefore underestimated as it is only based on 74.5% of its value. As a result, the overall dialysis cost is also underestimated as it is calculated using a weighted average cost of HD and peritoneal dialysis (PD), where the weights are respectively 74.5% and 9.8%.

Moreover, the ERG base case applies an average cost of dialysis that accounts for the proportion of patients "not on dialysis" on all model cycles, instead of the first 4 cycles (2 years) of the model only, as described in the ERG's report. In the ERG's model, when the NHSBT dialysis status distribution is selected, the ICER increases to [redacted](with all other "Company base case" inputs remaining unchanged). The correction of both these assumptions leads to an ICER of [redacted]

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4.1.2. HD carer disutility for Li et al. (2017) applied to transplant patients

When the ERG implemented a HD carer disutility for Li et al. in the imlifidase and in the comparator arms, it seems that it was also implemented in the "Transplant" health state.

However, this has no impact on the ERG's base case model as they have used another source of data for the utility.

4.1.3. Transplant procedure cost

The costs of the transplant procedure in the ERG's model were applied to both patients who received a kidney graft following imlifidase and to patients who remain on dialysis. Note that in the ERG comparator group, the cost of the transplant procedure was only applied to the transplant patients. As a result, when the proportion of imlifidase patients receiving a kidney transplant is set to 96.3% in the ERG's model, the cost of transplant procedure is still applied to 100% of patients, leading to an ICER of [redacted]. When this is corrected, the ICER is [redacted]

4.1.4. Inconsistency in the implementation of the transplant-related AE costs:

The ERG mentioned that there was an error in the "company base case" model because the transplant-related AEs were applied to the half cycle corrected population and transplant-related AEs should have been applied to all patients receiving the transplant. The ERG has therefore made the correction in the imlifidase arm. However, the same correction was not applied in the ERG comparator arm, where the transplant-related AEs are still applied to the half cycle corrected population. When this error is corrected and the scenario where the comparator "dialysis" is switched to the ERG comparator the ICER decreases from [redacted] to [redacted]

In summary, addressing the modelling issues raised by Hansa above, in Section 4.1, the ERG's base case model ICER decreases from [redacted] to [redacted]

4.2. Cost-effectiveness model adaptations following NHSBT data analyses

Hansa initially proposed the transplant rate for the comparator arm was 0%, by definition of the eligible patient population being highly sensitized and unlikely to be transplanted. In the ERG model the lifetime transplant rate in the comparator arm was set to 31.44%, based on

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recent NHS Blood and Transplant data, and more reflective of changes to the Kidney Offering Scheme algorithm that prioritises people who are more highly sensitised.

Hansa concurs with the ERG that a compatible transplant may occur in a very small proportion of the comparator population, however Hansa does not agree with the method of implementation of the compatible transplant rate, nor with the 31.44% model transplant rate. The 31.44% used by the ERG is based on an annual probability of 17.2% calculated on the transplant rate of patients with a cRF≥99% using NHSBT data from 2015 to 2020, which is then applied on the first two years of the model. The ERG implemented a model transplant rate of 31.44% at the time of model entry due to the previous model structure that considered no compatible transplant for patients on dialysis. Applying a transplant rate at model entry does not account for the mortality within the dialysis arm.

As a result, Hansa recommends that the annual percentage of compatible-transplanted patients used in the model is [redacted]This is based on the NHSBT data analyses which demonstrates that the transplant rate for the proposed eligible patient population (see Section 1.2) was [redacted] over a period of 19 months - please see Appendix 7.1 for the subsequent calculation of the weighted average transplant rate of [redacted]

Hansa also maintained the ERG's assumption that the patients in the comparator group would be eligible for a compatible transplant within the first two years of the model. However, instead of converting the annual probability into a probability at model entry, as was the case in the ERG model, it was converted into a cycle-probability and implemented in the first four cycles (two years) of the model.

In regard to the proportion of patients in the comparator who received dialysis, the inclusion of the dialysis status distribution reported by NHSBT, most notably allows a proportion of patients in the comparator arm to receive no dialysis.

Hansa proposed an eligible patient population for imlifidase, as mentioned in section 0 and included a criterion that the patient should be on the transplant waiting list for at least two

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years to allow the time for the kidney offering scheme to find a suitable organ without the requirement for imlifidase. Moreover, a Matchability Score of 10 is one of the criteria for prioritisation of a patients in Tier A and it is estimated that the proportion of patients in Tier A and on the waiting list for ≥ 2 years who are not on dialysis is very small or zero. In our modified base case, we have therefore set this as zero percent.

Hansa believes that in line with the revised eligible patient population definition (see Section 1.2) there will be no eligible patients for imlifidase who have not yet received dialysis, therefore have set this percentage to zero in the revised base case but has maintained the NHSBT dialysis modality distribution.

4.3. NICE and ERG uncertainties raised and model adaptations

Firstly, in Hansa's base case, the Liem et al. (2008) paper was used for utility calculations and Li et al. (2017) was used as a scenario analysis. The appraisal committee and clinical experts attending the meeting suggested that Li et al. (2017), or Cooper et al. (2020) were to be used as the source for utility data. Cooper et al. is more recent and features longitudinal estimates, but Li et al. is UK specific and better reflects clinical practice. As a result, Hansa's model includes Li et al. (2017) data (7) as the base case model to better reflect the UK specific clinical practice.

The ERG considered that 96.3% would be a more appropriate assumption for the percentage of patients that were transplanted following imlifidase treatment as opposed to 100% used in Hansa's initial model. This ERG assumption accounts for the two patients out of fifty-four who did not receive the full licensed treatment dose of imlifidase.

As a result, Hansa has modified its base case model, implementing the assumption that 96.3% of the imlifidase patients have a subsequent transplant. The remaining patients enter the model in the dialysis health state.

NICE also requested that protocols be put in place in case a negative crossmatch is not achieved after imlifidase treatment and therefore another person on the waiting list has a chance of receiving a transplant, as a back-up plan. It is already accepted clinical practice to

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have a back-up recipient in place, and it appears in the detailed proposed care pathway in annex 1.

In regard to the distribution of dialysis modalities (haemodialysis vs. peritoneal dialysis) the ERG assumption applied the NHSBT data for patients with a cRF≥99% for the distribution of the dialysis modalities (haemodialysis vs. peritoneal dialysis), whereas the company base case applies the UK renal registry data for the distribution of the dialysis modality distribution.

Hansa agrees with the use of the NHSBT data for patients with a cRF ≥99% but does not agree with the inclusion of the patients that do not receive dialysis and has therefore modified the base case accordingly.

In addition, the ERG used Thomas et al, 2015 for caregiver disutility, applying it only to 90% of HD patients, while the company base case uses a Japanese reference and 100% caregiver disutility. Hansa agree with the ERG assumptions and therefore have modified the model to incorporate Thomas et.al, 2015 caregiver disutility data and have applied it only to 90% of the HD patients.

The ERG was also concerned with the high cost assigned to HD travel by ambulance, with the suggestion of redistributing the proportion of patients from ambulance to other NHS cost incurred transport. As a result, Hansa has modified the base case to exclude ambulance transportation from the distribution of NHS incurred transport.

The ERG has also raised concern regarding the exclusion of crossmatch test costs from within the model, therefore Hansa has now applied the cost of one crossmatch test following each full dose of imlifidase. Another cost not included in Hansa's model was for DSA tests, Hansa anticipate the rate of testing to be consistent with existing BTS guidelines for patients who have undergone de-sensitisation prior to transplant; at least once in the first 12 months. Therefore, DSA and crossmatch tests costs have now been included in the revise base case.

The ERG also highlighted that average patient weight used (75kg) was from a Welsh study in 2009, however in Hansa's clinical trials the average weight of patients was 69kg and so applied this for consistency with the costing of imlifidase, which uses actual patient weights.

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Consequently, Hansa has now also applied the average weight of patients from the clinical studies (69kg).

Finally, as mentioned in section 3.5, Hansa has used the graft survival predictions based on the newly published 3-year follow up data instead of the iBox for the graft survival extrapolations, selecting the population of the unlikely to be transplanted that are closer in patients' characteristic to the suggested population eligible to imlifidase described in Section 1.2. Please see section 7.2 for a comparison of the graft survival predictions.

In conclusion, the implementation of these changes has influenced the ICER and have been represented in Hansa's revised base case, summarised in section 5 below.

5. Hansa revised base case

Hansa have revised its cost-effectiveness model, utilising the NHSBT transplant rates for the eligible patient population and addressing the uncertainties raised in the letter from NICE and the ERG report (section 4). Moreover, the model has been updated with NHS reference costs from the recent 2021 publication. The revised Hansa base case ICER can be seen in Table 2 The different ICER scenariosTable 2.

Table 2 The different ICER scenarios

Scenario	ICER (including a XXX simple PAS discount)
Hansa Base Case (Sept 20)	[redacted]
ERG Base Case (Apr 21)	[redacted]
Hansa Revised Base Case – based on new evidence, confirmed population and revised assumptions	[redacted]

Based on the revised base case and NHSE&I/NICE feedback to minimise administrative burden, Hansa wish to propose a revised simple PAS discount totalling [redacted] which makes imlifidase a cost-effective treatment option for patients in England.

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Hansa looks forward to working with NICE to resume the NICE appraisal process, which was paused in March 2021, as efficiently as possible to ensure imlifidase is made available to appropriate patients in a timely manner. Hansa is willing to have a meeting with NICE, the ERG or NHSE&I if any further clarification is needed.

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7. Appendix

7.1. NHSBT data

The population of patients analysed was deceased donor transplants, post the implementation of the new KOS, from 1st October 2019 to 30th April 2021. The parameters explored include cRF (calculated reaction frequency): degree of sensitization, Matchability Score (MS): relative ease of good HLA match within donor population (1=easiest, 10=most difficult), sex (male v female), ethnicity BAME (Black, Asian & Minority Ethnic communities) or white, blood group (B v non-B) and waiting time (time on waiting list in years).

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The table below outlines the key information provided by NHSBT:

Patients active at 1 October 2019

NHS Blood and Transplant

Transplants included are any deceased donor transplants between 1 October 2019 and 30 April 2021

Matchability	Sensitisation	Patients Active	Transplanted	% Transplanted
8	85-94	73	34	46.6
	95-98	64	31	48.4
	99	40	16	40.0
	100	10	<5	20.0
9	85-94	79	47	59.5
	98	82	46	56.1
	99	75	18	24.0
	100	159	36	22.6
10	85-94	15	7	46.7
	95-98	22	9	40.9
	99	35	12	34.3
	100	425	45	10.6

The data does not attempt to censor for any patients that have been removed from or died on the list, or received a living donor transplant. All deceased donor transplants that took place between 1 October 2019 and 30 April 2021 are included in the totals, including those offered via the fast track scheme or via centre based offering between 31 March 2020 and 16 June 2020.

Of the 425 patients with a cRF=100% and MS=10, [redacted] received a transplant over this 19-month period. Of the 35 patients with a cRF=99% and MS=10, [redacted] received a transplant over the same period.

Applying a weighted average, we derive from this data that patients with a cRF ≥99% had a [redacted] chance of being transplanted over this 19-month period. Engagement with clinicians regarding this data suggests that this [redacted] can be considered “unlikely to be transplanted”. This converts into a transplant rate of [redacted] over a period of one year, assuming an exponential distribution.

7.2. Extrapolation of graph survival following an imlifidase transplant

Figure 3 shows the three model options for graft survival at the moment of the model submission in September 2020: prediction using the iBox data, along with the predictions using extrapolations on the two populations: “All imlifidase” and the “unlikely to be transplanted.” iBox was used in the model to account for the different patient characteristics at 6 months post-transplant, but was also the most conservative approach. Figure 4 shows

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that the gap between iBox and the actual predictions using extrapolations of the two populations had increased on the updated analysis using a more recent data cut-off.

Figure 3 Graft survivals derived from the imlifidase trials, in the September 2020 model

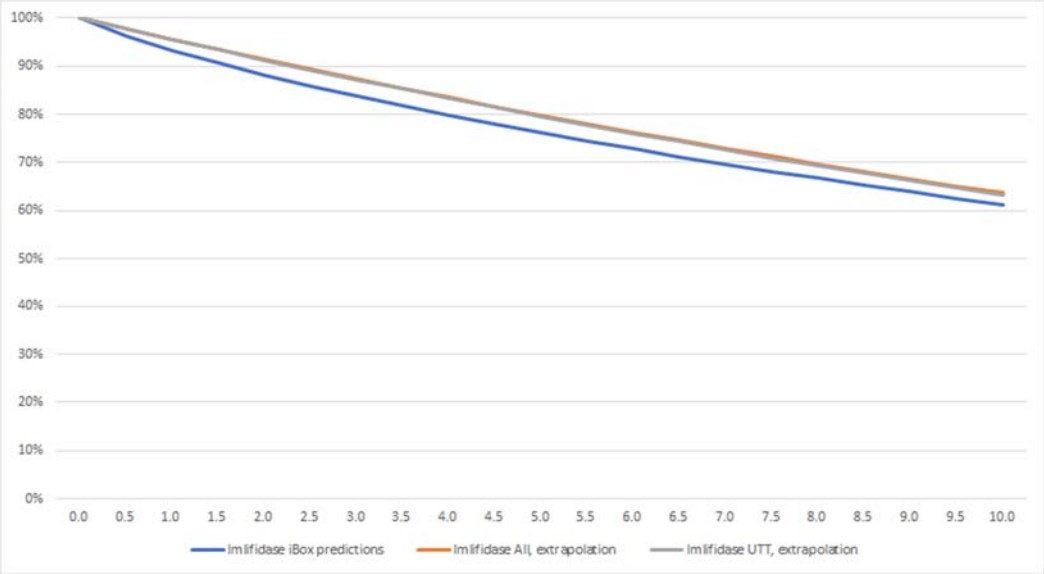

Figure 4 Graft survivals derived from the imlifidase trials, in the October 2021 model

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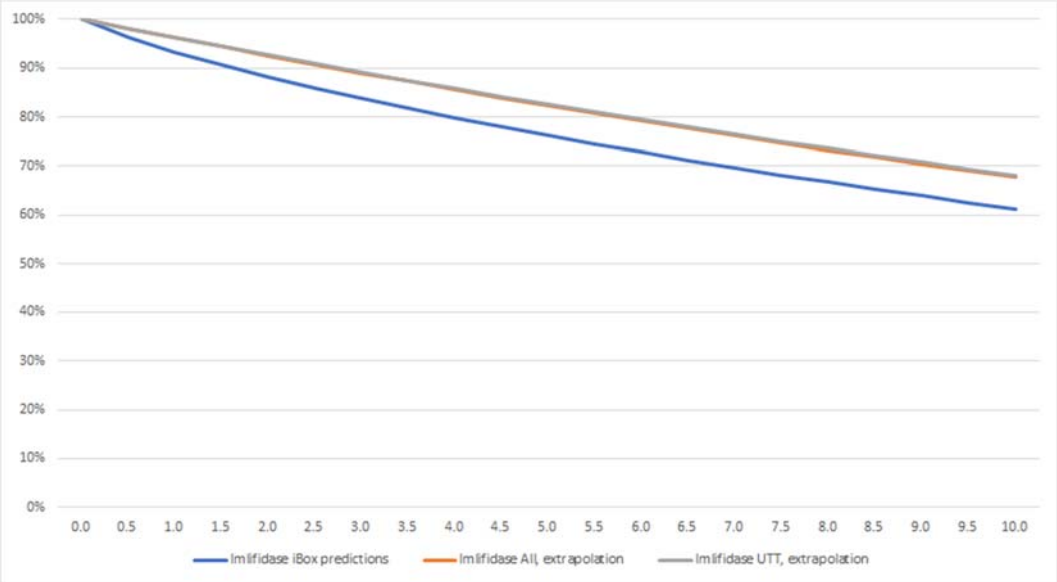

7.3. Data presentation

The ERG highlighted that Hansa Biopharma could have provided the clinical-effectiveness data in a way that would have given greater confidence in the findings. The committee acknowledged that Hansa Biopharma had provided all the data it had available at that point but agreed with the ERG that the data could have been presented in a more meaningful way to allow for validation. There were 6 main areas where amends were suggested, please see below how these have been addressed:

1. Rates of crossmatch conversion, specifying the test and length of follow up. Ideally, separate rates for each type of test individually, because of known variation in the sensitivity or specificity. Length of follow up with variance should also be reported, and it would be useful to have rates reported at timepoints that would be informative to conceptualise the treatment pathway for imlifidase (for example 2 hours, 4 hours, 6 hours, 8 hours and so on).

Response:

Flow cytometry crossmatch (FCXM) was used for determining the crossmatch conversion. Complement-dependent cytotoxicity crossmatch (CDCXM) is less sensitive than FCXM and will be converted within 1h since single cleaved IgG (scIgG) have heavily attenuated effect on

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complement binding (8) CDCXM was confirmed to be converted for 8 patients, no post-imlifidase dose CDCXM has been positive. So, when Hansa has been discussing crossmatch conversion it has always been the intention to convert both B- and T-cell FCXM from positive to negative. The clinical studies have not been designed to capture the time to crossmatch conversion, they have focused on the "within 24h" timeframe. See
Table 3 for the data on the patients regarding time to crossmatch conversion.

At this time Hansa would recommend that multiple crossmatch tests are performed over time. Suggestion is to test at 2h and 4h and proceed to transplant as soon as the crossmatch is converted. If the 4h is positive give a 2nd dose and then test 2h post 2nd dose. This is the crossmatch testing schedule that will be used in the Post-Authorisation Efficacy Study (PAES).

Table 3 Time to crossmatch conversion in studies 03, 04 and 06

Time to Conversion	Number of patients (%), in studies 03, 04 and 06	Number of patients (%), cPRA ≥ 99	Number of patients (%), cPRA =100%
Negative pre-dose	[redacted]	[redacted]	[redacted]
Not tested post-dose	[redacted]	[redacted]	[redacted]
Less than 1h	[redacted]	[redacted]	[redacted]
Less than 2h	[redacted]	[redacted]	[redacted]
Less than 6h	[redacted]	[redacted]	[redacted]
Less than 24h	[redacted]	[redacted]	[redacted]
2-6h	[redacted]	[redacted]	[redacted]
6-15.7h	[redacted]	[redacted]	[redacted]

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6-24h	[redacted]	[redacted]	[redacted]
2-24h	[redacted]	[redacted]	[redacted]
Not converted [C]	[redacted]	[redacted]	[redacted]

[A] Negative at first tested timepoint post-dose

[B] These patients were given a 2nd dose, none of them were tested pre 2nd dose, thus were not confirmed to need the 2nd dose for conversion.

[C] the patient was borderline positive and then virtual crossmatch was negative, so the patient proceeded to transplantation.

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2. Mean or median change (both if possible) in mean fluorescence intensity levels specific to donor-specific antibodies accompanied by variance data.

Response:

See Table 4 with requested MFI (immunodominant DSA) for all transplanted patients, Table 5 for patients with cPRA≥99% and for patients with cPRA=100% in Table 6.

For specific analysis of subpopulations, the subpopulations must be given.

Table 4 Summary of MFI for immunodominant DSA for all transplanted patients

Timepoint (n)	MFI all transplanted, mean (SD)	MFI all transplanted, median (range)
Predose [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]

Table 5 Summary of MFI for immunodominant DSA for cPRA ≥ 99%

Timepoint (n)	MFI all transplanted, mean (SD)	MFI all transplanted, median (range)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]

Table 6 Summary of MFI for immunodominant DSA for cPRA = 100%.

Timepoint (n)	MFI all transplanted, mean (SD)	MFI all transplanted, median (range)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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3. Rate of transplant rejection, rate of acute and chronic antibody-mediated rejection, number of cases of antibody-mediated rejection resolved by 6 months, number of cases of antibody-mediated rejection that resulted in graft loss.

Response:

See results of summary of rejections, AMR chronic AMR and Hyperacute rejection for all transplanted patients in Table 7, for patients with cPRA≥99% in Table 8 and for cPRA=100% in Table 9.

Table 7 Summary of Rejections for all transplanted patients

All (n=46)	Rate	Resolved, by 6 months	Rejection leading to graft loss
Rejections (not borderline CMR)	[redacted]	[redacted]	[redacted]
AMR	[redacted]	[redacted]	[redacted]
Chronic AMR	[redacted]	[redacted]	[redacted]
Hyperacute rejection (non-IgG)	[redacted]	[redacted]	[redacted]

Table 8 Summary of Rejections for cPRA ≥ 99%

cPRA ≥ 99% (n=29)	Rate	Resolved, by 6 months	Rejection leading to graft loss
Rejections (not borderline CMR)	[redacted]	[redacted]	[redacted]
AMR	[redacted]	[redacted]	[redacted]
Chronic AMR	[redacted]	[redacted]	[redacted]

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Hyperacute rejection (non-IgG)	[redacted]	[redacted]	[redacted]

Table 9 Summary of Rejections for cPRA = 100%

cPRA = 100% (n=25)	Rate of rejection	Resolved, by 6 months	Rejection leading to graft loss
Rejections (not borderline CMR)	[redacted]	[redacted]	[redacted]
AMR (including chronic)	[redacted]	[redacted]	[redacted]
Chronic AMR	[redacted]	[redacted]	[redacted]
Hyperacute rejection (non-IgG)	[redacted]	[redacted]	[redacted]

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4. Time to event data for the rebound of donor-specific antibodies after transplant, and variance around the rise in mean fluorescence intensity levels reported at timepoints in the company submission (day 7 to day 30).

Response:

This depends on the definition of "rebound", which to Hansa's knowledge is not standardized and there is no clear definition of rebound. Hansa has in this analysis defined rebound as: time to start of increase and/or at least passing 1000 MFI. Due to lack of timepoints, to exactly define when the rebound occurred in relation to imlifidase dosing the time was visually approximated from graphs of individual patients DSAs. Results are presented in Table 10

For variance of the data and the MFI levels see Table 4, Table 5 and Table 6.

Table 10 Days to DSA rebound, visually approximated

Time to DSA rebound	All transplanted (N=46)	≥99% cPRA (N=29)	100% cPRA (N=25)
Less than 4 days	[redacted]	[redacted]	[redacted]
4-7 days	[redacted]	[redacted]	[redacted]
Approx. 10 days	[redacted]	[redacted]	[redacted]
Approx. 14 days	[redacted]	[redacted]	[redacted]
>14days	[redacted]	[redacted]	[redacted]
No DSA post-dose	[redacted]	[redacted]	[redacted]

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5. Proportion needing treatment for the rebound of antibodies after transplant at multiple timepoints which would inform decision making (for example, 48 hours, 1 week, 1 month, 6 months), and the nature and timepoint of treatment.

Response:

Data have not been collected to capture if the treatment is related to “rebound of antibodies”. However, treatment for “graft rejection treatment” (regardless of biopsy status) is the best available data, this would include all suspected AMR (and therefore potentially treated to reduce DSA) and confirmed AMR, but it also includes treatment for CMR. In general, high DSA was not treated unless clinical signs of rejection were present. See Table 11 for proportion and treatments (protocol defined medications are not included).

Table 11 Treatments of graft rejection treatment. Note that patients can be in multiple groups if treated over time

Time	N patients needing treatments	Type of treatment
within 1 week	3 (7%)	Methylprednisolone (n=3)
1 week to 2 weeks	12 (26%)	rATG (n=3), Bortezomib (n=1), Eculizumab (n=5), Methylprednisolone (n=6), Plasmapheresis (n=5), Rituximab (n=1)
2 weeks to 1 month	8 (17%)	rATG (n=2), Bortezomib (n=1), Eculizumab (n=4), Immunoadsorption (n=1), Immunoglobulin human normal (n=3), Methylprednisolone (n=4), Plasmapheresis (n=4), Rituximab (n=1), Splenectomy surgery (n=1), Splenic embolization (n=1)

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1 months to 3 months	10 (22%)	rATG (n=1), Eculizumab (n=3), Immunoglobulin human normal (n=8), Methylprednisolone (n=7), Plasmapheresis (n=5), Prednisone (n=1), Rituximab (n=1)
3 months to 6 months	10 (22%)	Eculizumab (n=1), Immunoglobulin human normal (n=5), Methylprednisolone (n=4), Mycophenolate mofetil (n=1), Plasmapheresis (n=1), Prednisone (n=1), Rituximab (n=1)

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6. Rate of infection (overall and treatment-related) because it would be useful to see how many of the those who had a second dose exhibited an infection.

Response:

The most relevant infection rates are cited in the latest SmPC. The most common serious adverse reactions in clinical studies were pneumonia (5.6%) and sepsis (3.7%). The most common adverse reactions were infections (16.7%) (including pneumonia (5.6%), urinary tract infection (5.6%) and sepsis (3.7%) The subgroups ≥99% cPRA and 100% cPRA did not differ significantly. The SmPC also cites the following adverse events as commonly occurring (≥1/100 to <1/10): Abdominal infection, Adenovirus infection, Catheter site infection, Infection, Influenza, Parvovirus infection, Pneumonia, Postoperative wound infection, Sepsis, Upper respiratory tract infection, Urinary tract infection and Wound infection (4).

No difference was seen in between the transplanted patients that received a 2nd dose of 0.25mg/kg (data limited to 3 patients) and the ones receiving one dose. There is only minor difference reduction of the total level of IgG between 1 and 2 doses (9) and the 3 patients that received a 2nd dose and was transplanted were given IVIG relatively shortly (1 week) after dosing. One patient was transplanted after receiving 2 doses of 0.12mg/kg, but C_{max} (determines the maximal IgG decrease) of imlifidase is lower for that than a single dose of 0.25mg/kg (9).

7.4. PAES endpoints

Endpoints:

Primary endpoint
• 1-year graft failure-free survival in patients who have been kidney transplanted after imlifidase treatment
Secondary endpoints relating to imlifidase treatment

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- Renal function at several time points between 24 hours and 2 weeks and at 1, 3 and 6 months and 1 year after transplantation as assessed by estimated glomerular filtration rate (eGFR) and serum/plasma creatinine levels
- Patient survival at 1 year after transplantation
- Graft survival at 1 year after transplantation
- Proportion of patients with conversion of a positive crossmatch test to negative within 24 hours after imlifidase treatment
- HLA/DSA antibody levels at several time points between pre-dose imlifidase and 2 weeks, and at 1, 3 and 6 months and 1 year after imlifidase treatment
- Imlifidase PK up to 14 days after imlifidase treatment
- Imlifidase PD up to 9 days after imlifidase treatment
- ADAs up to 1 year after imlifidase treatment
- Frequency of DGF
- Proportion of patients with biopsy- and serology (DSA)-confirmed AMRs over 1 year
- Proportion of patients with biopsy confirmed CMRs over 1 year.
- Safety over 1 year as measured by reported SAEs
- Safety assessed as proportion of patients with infusion-related reactions within 48 hours of imlifidase infusion
- Safety assessed as proportion of patients with severe or serious infections within 30 days after transplantation

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• Change in patient-reported life participation, as measured by the PROMIS Social Health domain “Ability to participate in social roles & activities, PROMIS-SF-8a”, from baseline to 1 year after transplantation
Secondary endpoints relating to the non-comparative concurrent reference cohort
• Graft failure-free survival at 1 year after transplantation • Renal function at 1, 3 and 6 months and 1 year after transplantation as assessed by eGFR and serum/plasma creatinine levels • Patient survival at 1 year after transplantation • Graft survival at 1 year after transplantation • Frequency of DGF • Proportion of patients with biopsy- and serology (DSA)-confirmed AMRs over 1 year • Proportion of patients with biopsy confirmed CMRs over 1 year • Safety over 1 year as measured by reported SAEs • Safety assessed as proportion of patients with severe or serious infections within 30 days after transplantation • Change in patient reported life participation, as measured by the PROMIS Social Health domain “Ability to participate in social roles & activities, PROMIS-SF-8a”, from baseline to 1 year after transplantation
Secondary endpoints relating to the randomly selected non-comparative historical reference cohort retrieved from the CTS registry
• Graft survival at 1 year after transplantation

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• Renal function at 3 and 6 months, and 1 year as measured by serum/plasma creatinine category (<130 µmol/L, 130-259 µmol/L, 260-400 µmol/L and >400 µmol/L) (eGFR only available in selected patients) • Patient survival at 1 year after transplantation • Proportion of patients with rejection episodes (AMRs and CMRs) during the first post-transplant year in patients with a functioning graft at the end of the first post-transplant year
Exploratory endpoints relating to the imlifidase treatment group and the concurrent reference cohort
• Change in patient-reported anxiety, depression, fatigue, pain interference, physical function and sleep disturbance, as measured by the PROMIS-29 outcome measure, from baseline to 1 year after transplantation • Percentage score and change in percentage score in patient reported impact on ability to work as measured by WPAI:GH, from baseline to 1 year after transplantation • EQ-5D-5L dimension responses, EQ-5D-5L utility index score and EQ VAS score at baseline and 1 year after transplantation

Patients active at 1 October 2019

NHS Blood and Transplant

Transplants included are any deceased donor transplants between 1 October 2019 and 30 April 2021

Matchability	Sensitisation	Patients Active	Transplanted	% Transplanted
8	85-94	73	34	46.6
	95-98	64	31	48.4
	99	40	16	40.0
	100	10	<5	20.0
9	85-94	79	47	59.5
	98	82	46	56.1
	99	75	18	24.0
	100	159	36	22.6
10	85-94	15	7	46.7
	95-98	22	9	40.9
	99	35	12	34.3
	100	425	45	10.6

The data does not attempt to censor for any patients that have been removed from or died on the list, or received a living donor transplant. All deceased donor transplants that took place between 1 October 2019 and 30 April 2021 are included in the totals, including those offered via the fast track scheme or via centre based offering between 31 March 2020 and 16 June 2020.

Patients active at 1 October 2019 -Matchability Score 10 and cRF 100%

NHS Blood and Transplant

Ethnicity	N	Transplanted	% Transplanted
White	229	24	10.5
BAME	193	210	10.8
Not reported	<5		

Sex	N	Transplanted	% Transplanted
Male	198	26	13.1
Female	227	19	8.4

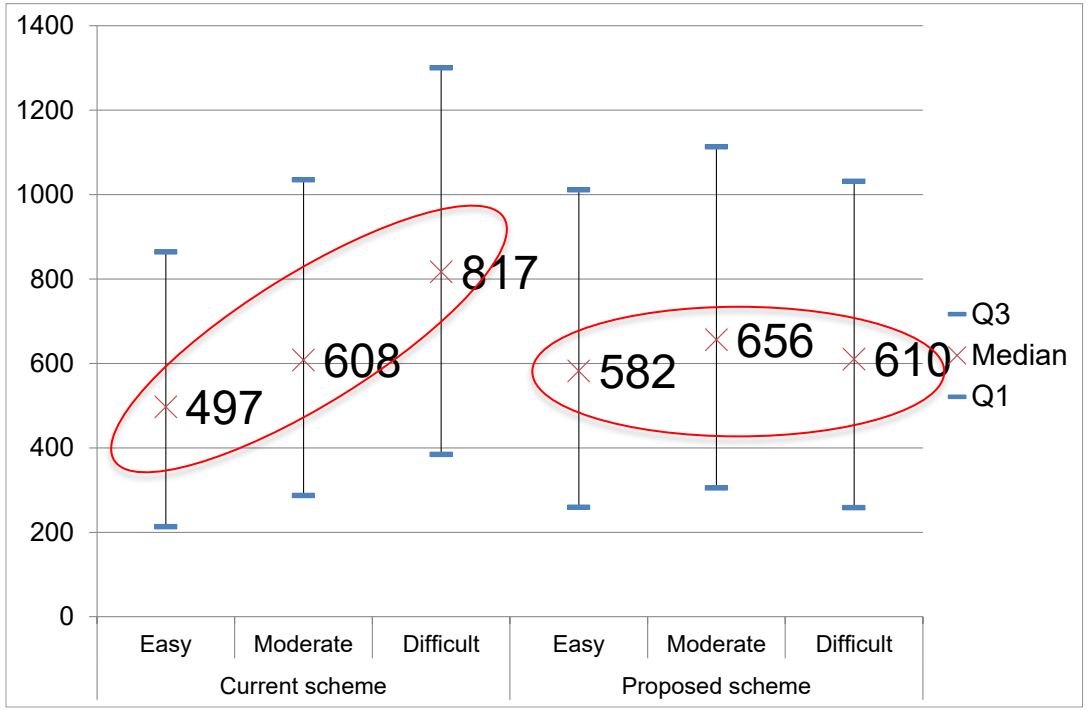
The data does not attempt to censor for any patients that have been removed from or died on the list, or received a living donor transplant. All deceased donor transplants that took place between 1 October 2019 and 30 April 2021 are included in the totals, including those offered via the fast track scheme or via centre based offering between 31 March 2020 and 16 June 2020.

Simulation Results - Matchability and cRF

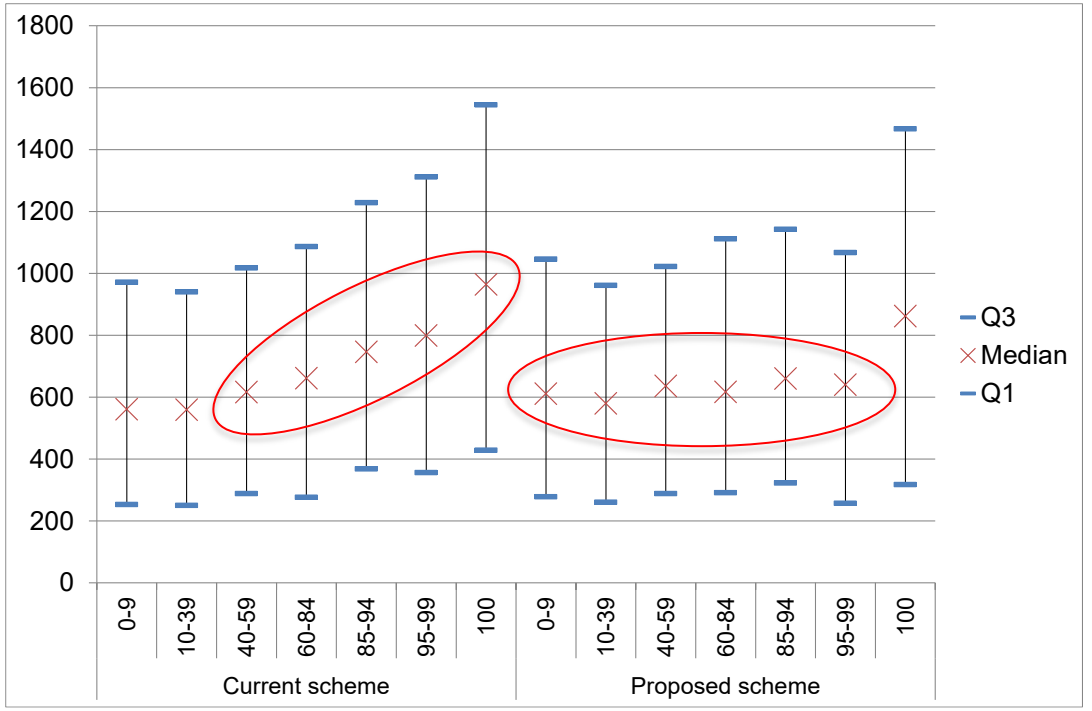
NHS Blood and Transplant

Waiting time on list end of year 4

Matchability



cRF

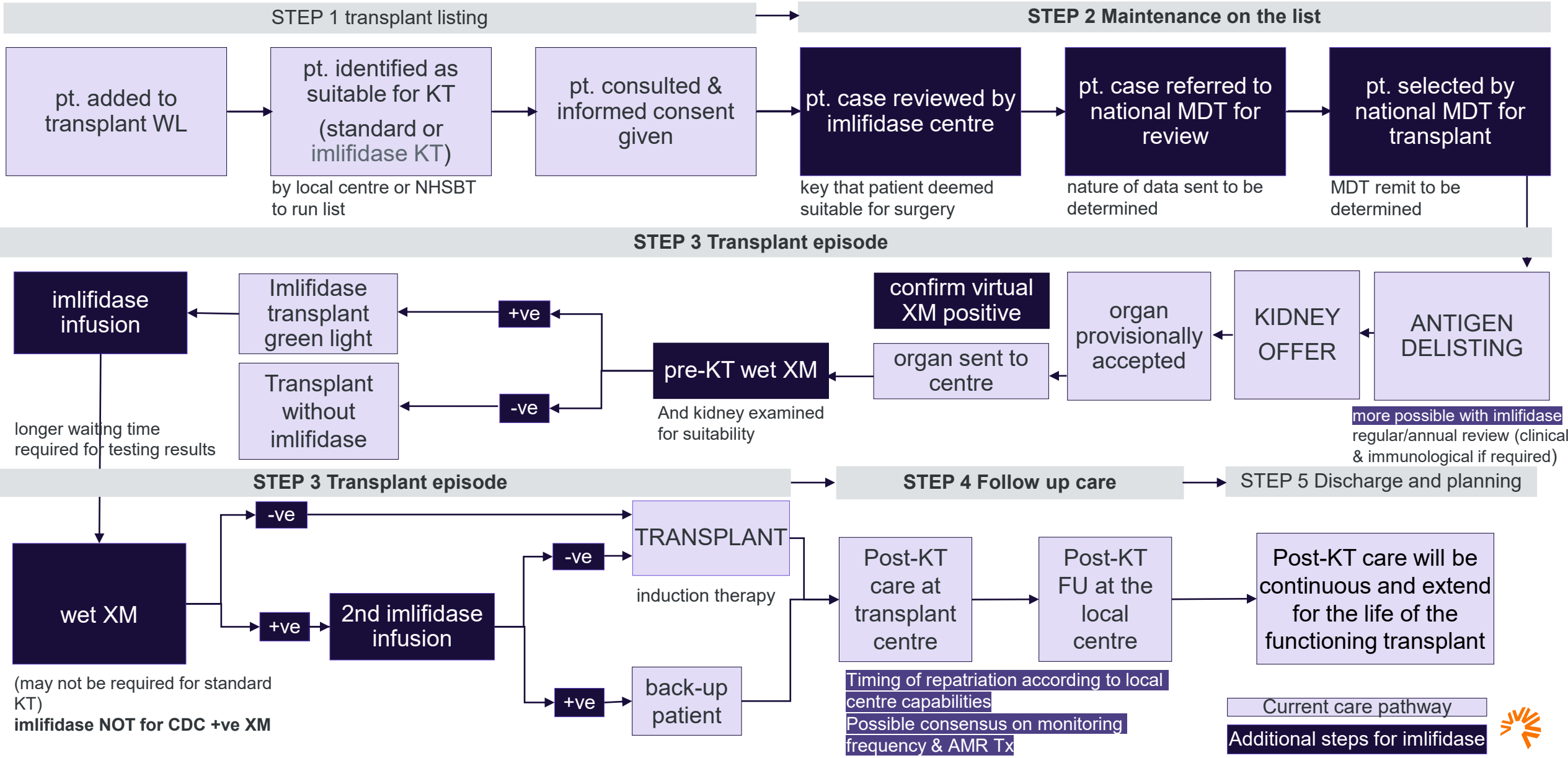


The proposed scheme

- Transplants more difficult to match and highly sensitised patients
- Reduces the variability in waiting time

Revised 22nd Nov 2021

The integration of imlifidase into the current care pathway



1 Abbreviations: AMR: antibody-mediated rejection; CDC: complementary dependent cytotoxicity; FU: follow-up; KT: Kidney Transplant; MDT: multidisciplinary team; NHSBT: NHS Blood and Transplant; pt: patient; tx: treatment; WL: waiting list; XM: crossmatch; -ve: negative; +ve: positive

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

Hansa response to ERG questions following additional evidence presented before ACM 2

22nd November 2021

Additional data

ERG question [Priority question] Please supply the data provided by NHSBT to support dialysis and transplant rates in the comparator population in the model.

Hansa response: The NHSBT data presented to Hansa by Dr Matthew Robb on 7th July 2021 was uploaded onto NICE docs on Wednesday 17th November. This is all the data that NHSBT provided to Hansa, in the PowerPoint presentation only.

Treatment pathway for imlifidase

- **Hansa response:** Hansa met with Ian Wren (Lead Commissioner for Renal Services at NHSE&I) in August 2021 as part of a NHSE&I clinical and commercial surgery, and on the 22nd November. During this last meeting we set out a plan to engage with relevant clinicians and experts to review and develop the imlifidase treatment pathway. We will ensure this work takes into account the ERG's questions on this topic, and will keep NICE informed of any amendments to the treatment pathway resulting from this work

- **ERG Question:** In the updated submission, figure 2 suggests that one crossmatch test will be carried out pre- and post- treatment with imlifidase. However, from elsewhere in the submission we understand that additional testing may be required. We have incorporated these additional tests into the pathway shown in **Error! Reference source not found.** below (page **Error! Bookmark not defined.**).
    - Do you agree that this figure more closely represents the likely treatment pathway for imlifidase in practice?
- **Hansa response?**
    - In our letter dated 8th October, figure 2 suggests that the initial crossmatch test is not carried out until the organ has been received by the transplanting centre. This indeed may not accurately reflect what the clinicians we have spoken to anticipate. Clinicians plan to carry out a virtual crossmatch prior to the organ's arrival, in order to shorten the time to first cross-match result. We have altered this flow chart accordingly and the current version of the treatment pathway is attached to this response.
    - In terms of how many crossmatches need to be carried out: At the minimum there will be a crossmatch test pre-imlifidase infusion, and a cross match test post-imlifidase infusion. In the event that the cross-match is not converted from positive to negative, there will be a second imlifidase infusion followed by a third crossmatch test. So the number of crossmatch test carried out will be 2 or 3.
    - The new Figure 1 includes the potentially greatest increases to timelines associated with the introduction of imlifidase into the pathway.
    - It is anticipated that in the imlifidase treatment pathway, a kidney is assigned and sent to a centre on the basis of a positive virtual crossmatch. It is considered unlikely that subsequently there would be a negative "wet" crossmatch result (which would thereby warrant a transplant to take place without an imlifidase infusion) once the organ is received at the centre.

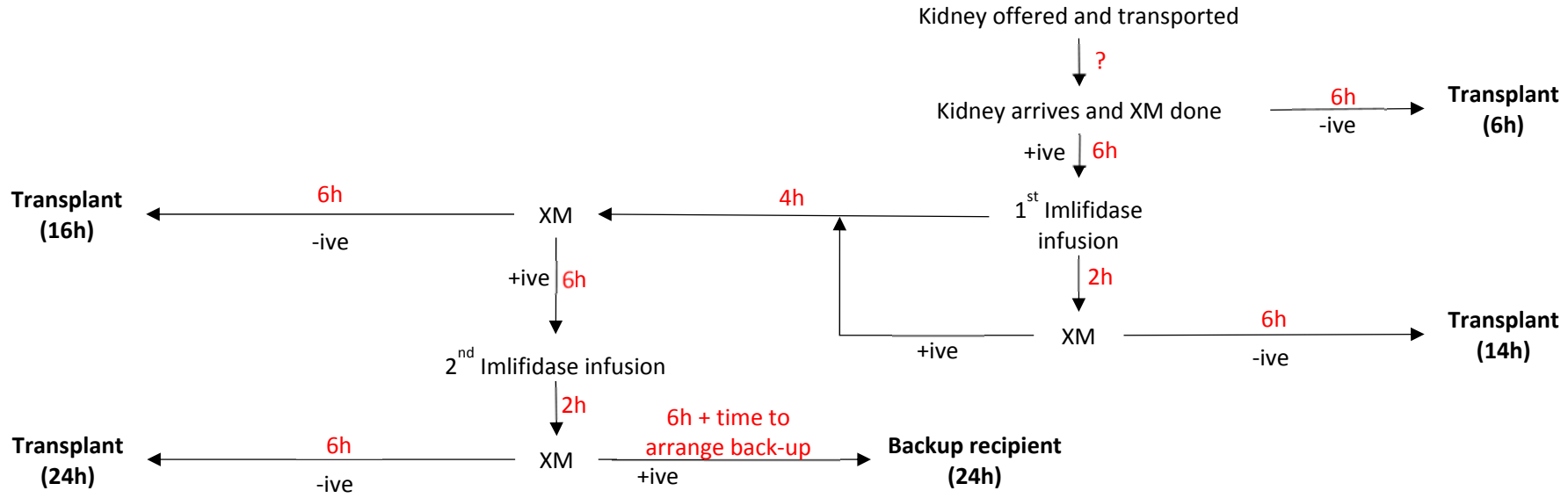
- **ERG Question:** Table 3 in the updated submission indicates that 20% of patients treated with imlifidase achieved crossmatch conversion between 6h and 24h post infusion. Despite this, the submission recommends crossmatch testing at 2h and 4h post-infusion.
    - Please explain the reasoning for this recommendation.
    - Will some patients taking longer than 4h for crossmatch conversion receive a 2nd dose where it may not have been necessary?
- **Hansa response:** The clinical experts whom we consulted (including Professor David Briggs, Head of Histocompatibility and Immunogenetics (H&I) laboratory, Queen Elizabeth Hospital Birmingham; Dr Sian Griffin, Consultant Nephrologist, University Hospital of Wales, and Senior Lecturer, Cardiff University; Professor Nithya Krishnan, Consultant Transplant Nephrologist, University Hospitals Coventry & Warwickshire NHS Trust; Dr Rommel Ravanan, Consultant nephrologist/Transplant Physician at North Bristol NHS Trust; and Dr Adnan Sharif, Consultant Nephrologist and Renal Transplant Physician, Birmingham) felt that the timing of cross match testing was appropriate based on clinical practice and available trial evidence. Hansa will continue to review timing of sampling for cross match testing with clinical experts and keep NICE informed of any amendments to the pathway.

- **ERG Question:** In appendix 7.3 of the updated submission it's noted that 2 patients received a 2nd dose of imlifidase despite not having been tested for a crossmatch conversion.
    - Why did these patients receive a 2nd dose?
    - Is the reported time to conversion for these patients reported from the 1st or 2nd dose?
- **Hansa response:** The reported time to conversion for these patients was from the 1st dose. As per the Jordan 2020 publication (Jordan et al, Transplantation 2021;105: 1808–1817), "Three patients received a second dose based on 2-h crossmatch assessments, all within ~13 h after the first dose.". Hansa will review this with clinical experts and keep NICE informed of any amendments to the pathway.

- **ERG Question**: Section 2.2 states that imlifidase could be integrated 'without increasing CIT'. Current average CIT in the NHS is 12-13 hours for DCD and DBD respectively.
    - Please explain the basis of the claim that this will not increase.
    - Our understanding is that in 20% of patients it takes 6-24h to achieve negative crossmatch, and that 3 to 4 crossmatch tests will be required (compared to the current single test), each taking 4-6 hours to receive the results. Please clarify if you consider this assumption to be incorrect.
- **Hansa response:** The clinical experts consulted felt that the proposed pathway would allow imlifidase-enabled transplants to be conducted within an acceptable cold ischaemia time (CIT). It is well recognised that CIT should be minimised, and the clinicians consulted indicated that they did not anticipate an untoward increase in this time with the inclusion of imlifidase in the pathway. Hansa will continue to develop the pathway with clinical experts to ensure CIT is minimised, and keep NICE informed of any amendments to the pathway.

- **ERG Question:** How long does the company envisage that it takes to receive the results of a wet crossmatch test? What is the source for this assumption?
- **Hansa response:** The UK clinical experts who collaborated with Hansa to develop the treatment pathway envisage to receive the crossmatch test results in 4 to 6 hours.

Figure 1: Proposed treatment pathway for imlifidase, incorporating additional testing requirements



Note: A 6h wait time for a crossmatch (XM) test is a conservative estimate based on feedback that it would take 4-6 hours for a final result

Revised patient population

- **Hansa response:**
  Please see table below outlining the criteria and study patient numbers for the "unlikely to be transplanted" patient analyses and the criteria for a new post-hoc analyses which Hansa has conducted to align with the proposed NICE eligibility criteria.

Table 1 Criteria for patients unlikely to be transplanted and new post-hoc analyses criteria

Unlikely to be transplanted (n=25)	New post-hoc (n=14)
• cPRA≥95% **and** • Deceased donor **and** • Positive crossmatch	• CRF≥99% **and** • Matchability score = 10 **and** • Dialysis ≥ 2 years **and** • Deceased donor **and** • Positive crossmatch

Please see Table 2 below which compares the trial evidence for the "All imlifidase", "unlikely to be transplanted" and "New post-hoc" groups. Hansa would like to note that due to the very small sample size of the new post-hoc analyses (n=14), outcome measure would be very sensitive to anecdotal events. Furthermore, there is significant overlap when the survival outcome confidence intervals for the three groups are compared.

- **ERG Question:** How many people in the available trial evidence for imlifidase meet the new proposed patient eligibility criteria?
- **Hansa response:** n=14, as detailed in Table 1

- **ERG Question:** Please can you clarify whether the group referred to in the updated submission as 'unlikely to be transplanted' are consistent with the new patient eligibility criteria (i.e., CRF≥99%, matchability score = 10, KOS waiting list≥2 years? If not, please provide a definition for this group
  - Is the cPRA 99% cohort in the new evidence consistent with the updated patient population? If not, what is the expected overlap?
- **Hansa response:** Please see **Hansa response** at the beginning of this section

- **ERG Question:** The submission requests that a multidisciplinary team establishes auditable criteria to ensure only those unlikely to receive a transplant will be treated with imlifidase. How does the company envisage these criteria will differ from the criteria presented by the company
- **Hansa response:** It is envisaged that the multidisciplinary team will review each potential patient individually in terms of eligibility for an imlifidase-enabled transplant. This assessment will include the criteria presented by Hansa in our letter dated 8th October, and further clinical considerations such as the predicted ability of the patient to withstand the potentially more aggressive immunosuppression regimen associated with such a transplant. Hansa will collaborate with NHSE&I and relevant clinicians to develop auditable criteria and will keep NICE informed.

- **ERG Question:** Please give the source for the assumption that zero patients will not receive dialysis. The ERG note that the population presented in the submission is not equivalent to 'Tier A' in the KOS as suggested in section 4.2
- **Hansa response:** The vast majority of patients who are on the transplant waiting list for ≥ 2 years will be receiving dialysis. To ensure equity within the allocation system, imlifidase should not be offered to patients who are not receiving dialysis and therefore to remove ambiguity, Hansa suggest amending the eligibility criterion to state: and been on the waiting list for 2 years or more *and currently receiving dialysis*. This criteria was included in order to allow sufficient time for a suitable match to be identified through the allocation algorithm prior to using imlifidase.

  Hansa wish to clarify that although the proposed eligibility criteria are not entirely equivalent to those of Tier A, all patients meeting these criteria would be classed as being in Tier A of the KOS due to their matchability score of 10 alone.

Clinical/model outcomes

- **ERG Question:** Can you please complete Table 2Table 2 below with as much clinical data as you have in the new patient population from the original trials and the 3-year follow-up study?
- **Hansa response:** Please see Table 2 completed, which has also been slightly modified to better align to the outcomes of the original trial and allow a robust analysis between the groups.

- **ERG Question:** In the same table below, we have added additional columns for data in the 'alternative most relevant population' from the original and 3-year follow-up trials. These data will be useful if some/all outcomes are not available in the new patient population. Please state which patient subgroup you consider this to be, and complete the table with the requested outcomes. While some of these data may be provided in the updated submission, some data points were not provided for all populations, or in a different format. The table will allow us to be clear about the data that are available, and provide data in a comparable format.
- **Hansa response:** Please see Table 2 below which compares the trial evidence for the "All imlifidase", "unlikely to be transplanted" and "New post-hoc" groups.

- **ERG Question:** Please can you also complete the outcomes in Table 2 for the 'all imlifidase' group. We appreciate that some of these outcomes have been provided elsewhere, however we are missing some of the data, and again it will be useful for us to have these data in a comparable format.
- **Hansa response:** The data has been added to Table 2

- **ERG Question:** Please provide KM curves with numbers at risk and number of censored patients for the 3-year follow up for graft survival and survival with a functioning graft for the "all imlifidase" and "unlikely to be transplanted" populations
- **Hansa response:** We have generated 3 figures for "All imlifidase" (Figure 2), "unlikely to be transplanted" (Figure 3) and "New post-hoc" (Figure 4). They contain KM curves (inc. N at risk

tables) for graft survival, graft failure-free survival (i.e. survival with functioning graft) and patient survival.

- **ERG Question:** Please provide AIC/BIC statistics for the extrapolations fit to the iBox data
- **Hansa response**: For the iBox predictions, we are not able to provide the AIC/BIC scores because the data were not extrapolated using individual patient data. They were extrapolated based on the iBox predictions at 10 different time points: Year 1 to Year 10 post-evaluation (with the evaluation performed at 6 months post-graft). In the model, a solver was used for each of the four 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. For this reason, the AIC/BIC were provided only for the extrapolations performed on the "All imlifidase" and the "Unlikely to be transplanted" populations.

- **ERG Question:** Please provide hazard function plots for graft survival and survival with a functioning graft for the "all imlifidase" and "unlikely to be transplanted" populations
- **Hansa response:** Hazard function plots have not been previously conducted and are not commonly required in this setting and Hansa would be interested to understand the rationale for the request. Hansa did not generate the plots due to the tight timelines however they can be provided post the meeting if still required.

- **ERG Question:** Please provide generalized gamma and Gompertz extrapolations for graft survival and survival with a functioning graft for the "all imlifidase" and "unlikely to be transplanted" populations.
- **Hansa response:** The generalized gamma and Gompertz extrapolations for graft survival and survival with a functioning graft for the "all imlifidase" and "unlikely to be transplanted" populations are presented in the attached spreadsheet. This spreadsheet also contains the AIC/BIC of the model distribution as well as those associated with Gompertz and generalized gamma.

- **ERG Question:** Please provide full base case results including total and incremental costs, QALYs and Lys
- **Hansa response**: Table 3 and Table 4, summarise the incremental, deterministic base case results of the cost-effectiveness analysis for imlifidase including a simple discount of [redacted] and [redacted] respectively, applied to the list price of £270,000 for two vials.

- **ERG Question:** Please provide updated OWSA and PSA results for the new company base case
- **Hansa response:** The probabilistic sensitivity analysis (PSA), mean and 95% confidence interval (CI), using a discount of [redacted] and [redacted] are presented in Table 5 and Table 6, respectively. Figure 5 and Figure 6 show scatter plots of the PSA iterations, while Figure 7 and Figure 8 present the cost-effectiveness acceptability curve for these two levels of discount. The one-way sensitivity analysis for the [redacted] and the [redacted] level of discount are presented inFigure 9 and Figure 10, respectively.

- **ERG Question:** Please provide scenario analysis results exploring the impact of the company base case key assumptions on the ICER

- **Hansa response:** Table 7 and Table 8 report the impact of the scenario analyses on ICERs, using a discount on imlifidase of [redacted] and [redacted] respectively.

PAES trial

- ERG Question: Does "[redacted] Please provide an exact definition for this endpoint.
- **Hansa response:** Both death and graft failure will be counted. The primary endpoint is graft failure-free survival (% of patients) 1 year after kidney transplantation post-imlifidase treatment. Graft failure is defined as permanent return to dialysis for at least 6 weeks, re-transplantation, or nephrectomy. Patients who die from any cause will also be considered as having had graft failure.

- **ERG Question:** PAES trial: EQ-5D states collection "at baseline and 1 year after transplantation", PROMIS-29 states collection "from baseline to 1 year after transplantation**".**
- **Hansa response:** The PROMIS-29 endpoint is: Change in patient-reported anxiety, depression, fatigue, pain interference, physical function and sleep disturbance, as measured by the PROMIS-29 outcome measure, from baseline to 1 year after transplantation. The EQ5D endpoint is: EQ-5D-5L dimension responses, EQ-5D-5L utility index score and EQ VAS score at baseline and 1 year after transplantation

- **ERG Question:** Are the two QoL measures on different schedules? If so why?
- **ERG Question:** At what time points will EQ-5D be collected?
- **ERG Question:** At what time points will PROMIS be collected?
- **Hansa response:** the two QoL measures are collected at the same time, at baseline (pre-screening) and at Year 1.

  ERG Question: Will data collection at 1 year still be collected in patients who have failed due to graft failure?
- **Hansa response:** Patients with graft failure will follow the same visits/samples as those with functioning grafts (some samples might not be possible due to the patients status of the patient). However, there might be patients who refuse visits due to no longer having functioning grafts. In such cases, patients who [redacted]

Table 2: Clinical outcome data requested from the company

	New post-hoc*	"unlikely to be transplanted"	'All imlifidase' population
Sample size	14	25	46
Overall rate of crossmatch conversion (x/X, %)	[redacted]	[redacted]	45 (98%)
Overall rate of crossmatch conversion using FACS (x/X, %)	[redacted]	[redacted]	45 (98%)
Number of patients who received 2 doses of imlifidase	[redacted]	[redacted]	4 (7%)
Total number of crossmatch tests conducted (only physical XM included, B or T-cell at same time counted as same test, CDC and FC counted as separate tests)	[redacted]	[redacted]	255 (5.5 tests per subject)
Total number of (FC) crossmatch tests conducted (only FCXM included, B or T-cell at same time counted as same test)	[redacted]	[redacted]	171 (3.7 tests per subject)
Number of patients who received a transplant after treatment with imlifidase (x/XX, %)	[redacted]	[redacted]	46 (100%)
Rate of AMR (x/XX, %), in Original trials	[redacted]	[redacted]	15 (33%)
Rate of chronic AMR (x/XX, %), in Original trials	[redacted]	[redacted]	4 (7%)
Rate of CMR (x/XX, %), in Original trials	[redacted]	[redacted]	10 (22%)
Rejection leading to graft loss (x/XX, %), in Original trials	[redacted]	[redacted]	1 (2%)
Number of patients receiving treatment for AMR (x/X, %), in Original trials	[redacted]	[redacted]	18 (39%)
Overall survival at final follow-up (x/X, %), in Original trials	[redacted]	[redacted]	46 (100%)
Enrolled in follow-up study	[redacted]	[redacted]	36
Rate of AMR (x/XX, %), in Follow-up trial	[redacted]	[redacted]	1 (3%)
Rate of chronic AMR (x/XX, %), in Follow-up trial	[redacted]	[redacted]	0 (0%)
Rate of CMR (x/XX, %), in Follow-up trial	[redacted]	[redacted]	0 (0%)
Rejection leading to graft loss (x/XX, %), in Follow-up trial	[redacted]	[redacted]	0 (0%)

	New post-hoc*	"unlikely to be transplanted"	'All imlifidase' population
Number of patients receiving treatment for AMR (x/X, %), in Follow-up trial	[redacted]	[redacted]	3 (8%)
Graft survival (median and 95%CI) at 6 months	[redacted]	[redacted]	93% (87%, 100%)
Graft survival (median and 95%CI) at 3 years	[redacted]	[redacted]	86% (75%, 99%)
Survival with functioning graft (median and 95%CI) at 6 months	[redacted]	[redacted]	93% (87%, 100%)
Survival with functioning graft (median and 95%CI) at 3 years	[redacted]	[redacted]	79% (67%, 94%)
Patient survival (median and 95%CI) at 6 months	[redacted]	[redacted]	No deaths
Patient survival (median and 95%CI) at 3 years	[redacted]	[redacted]	92% (83%, 100%)
Number of patients whose MFI levels remained above 3000 at all measured timepoints (x/XX, %)	[redacted]	[redacted]	1 (2%)
Rate of re-transplant (x/XX, %)	[redacted]	[redacted]	0 (0%)

* CRF≥99% **and** matchability score = 10 **and** Dialysis ≥ 2 years **and** DD **and** XM+

Figure 2 Kaplan-Meier curves for the "All imlifidase" group with number at risk tables. A) graft survival, B) graft failure-free survival and C) patient survival.

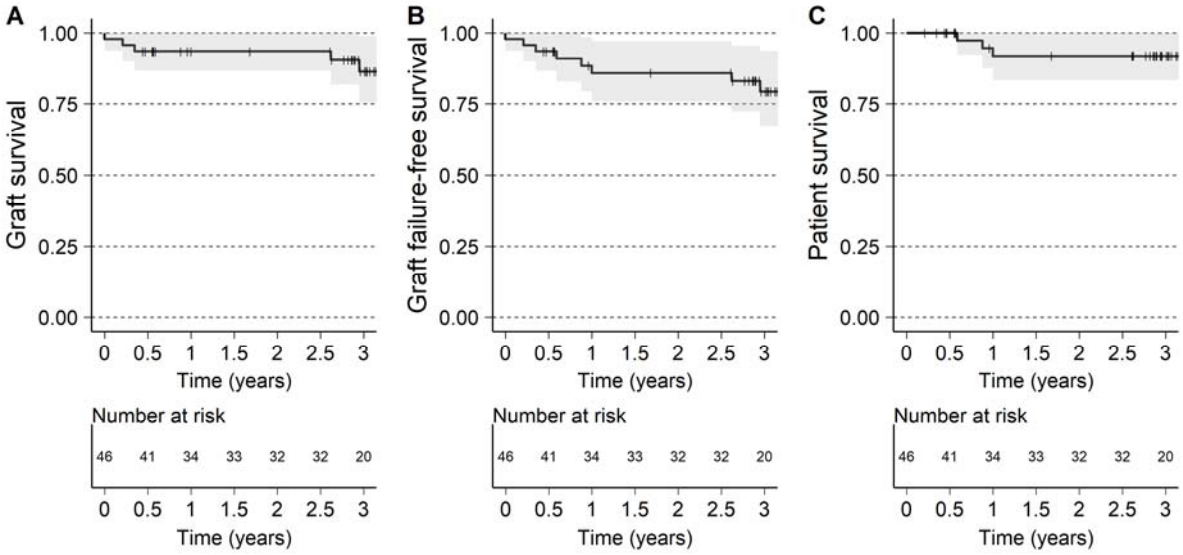


Figure 3 Kaplan-Meier curves for the "unlikely to be transplanted" group with number at risk tables. A) graft survival, B) graft failure-free survival and C) patient survival.

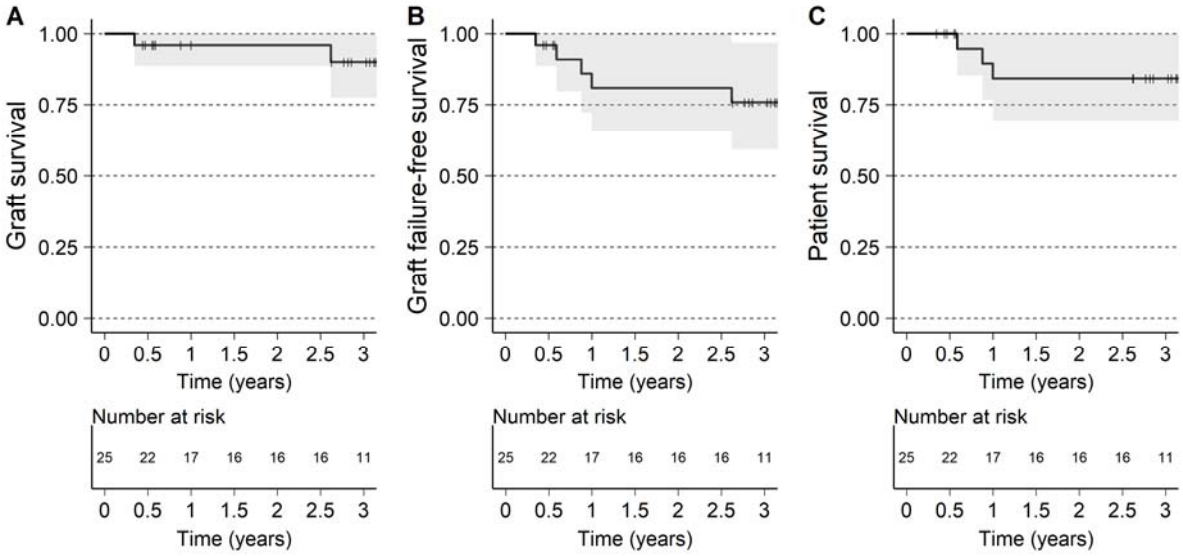


Figure 4 Kaplan-Meier curves for the "New post-hoc" group with number at risk tables. A) graft survival, B) graft failure-free survival and C) patient survival.

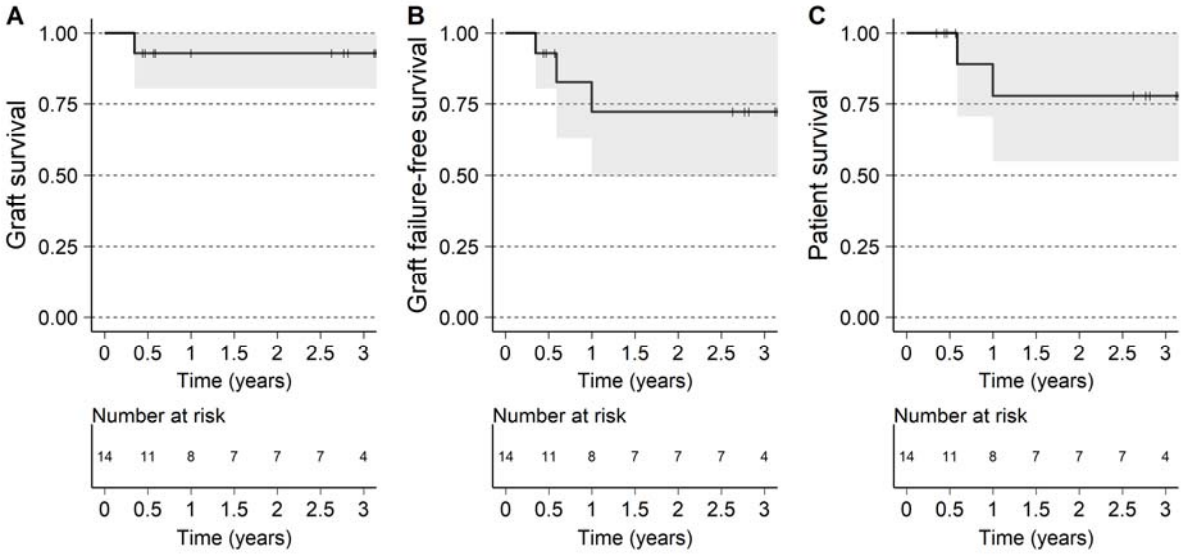


Table 3 Reference case deterministic results: X

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Imlifidase and transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,096
Dialysis	220,910	8.07	5.89				

Table 4 Reference case deterministic results: [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Imlifidase and transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,589
Dialysis	220,910	8.07	5.89				

Table 5 Reference case probabilistic results: [redacted]

	Costs (£)			QALY			ICER (£/QALY)
	Imlifidase and transplant	**Dialysis**	**Incremental**	**Imlifidase and transplant**	**Dialysis**	**Incremental**	
Reference case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,096
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,806
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,038
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	183,404

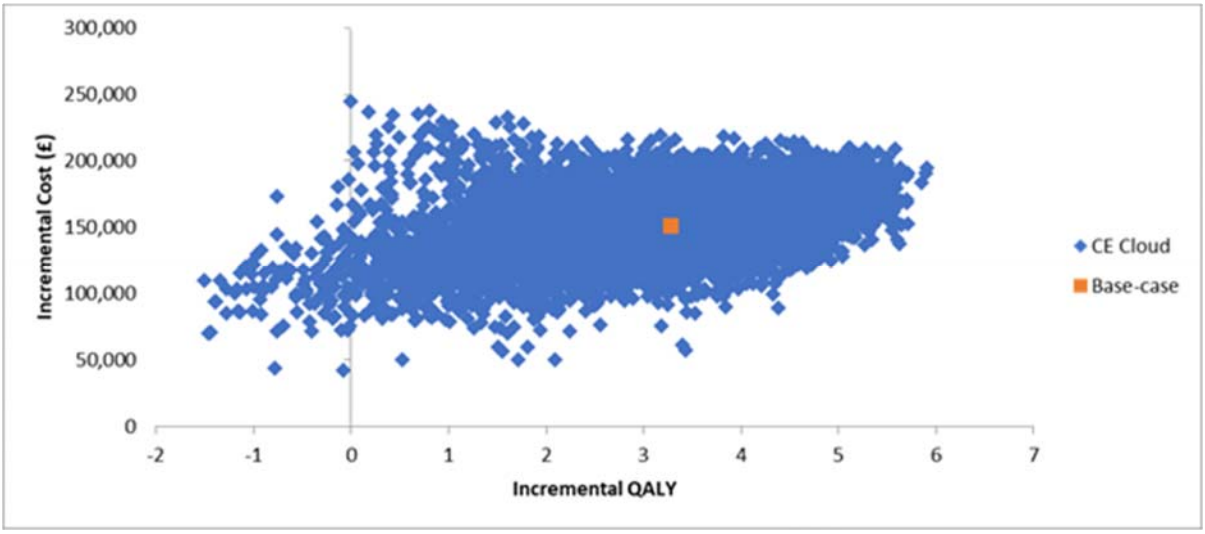
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; PSA, probabilistic sensitivity analysis.

Table 6 Reference case probabilistic results: X

	Costs (£)			QALY			ICER (£/QALY)
	Imlifidase and transplant	**Dialysis**	**Incremental**	**Imlifidase and transplant**	**Dialysis**	**Incremental**	
Reference case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,641
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,231
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,903
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	84,857

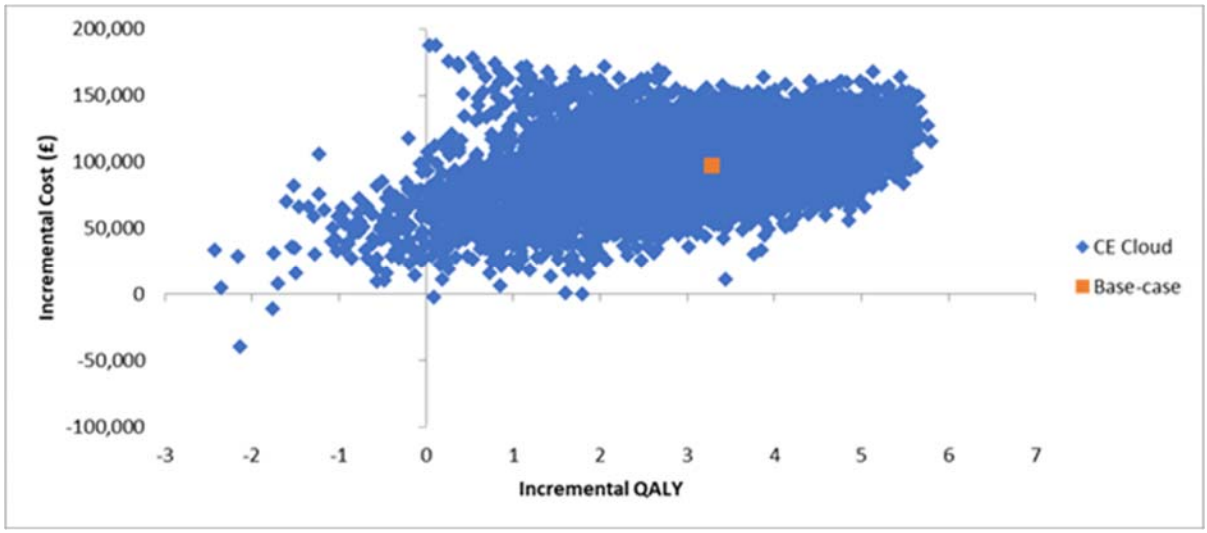
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; PSA, probabilistic sensitivity analysis

Figure 5 PSA scatter plot: [redacted]



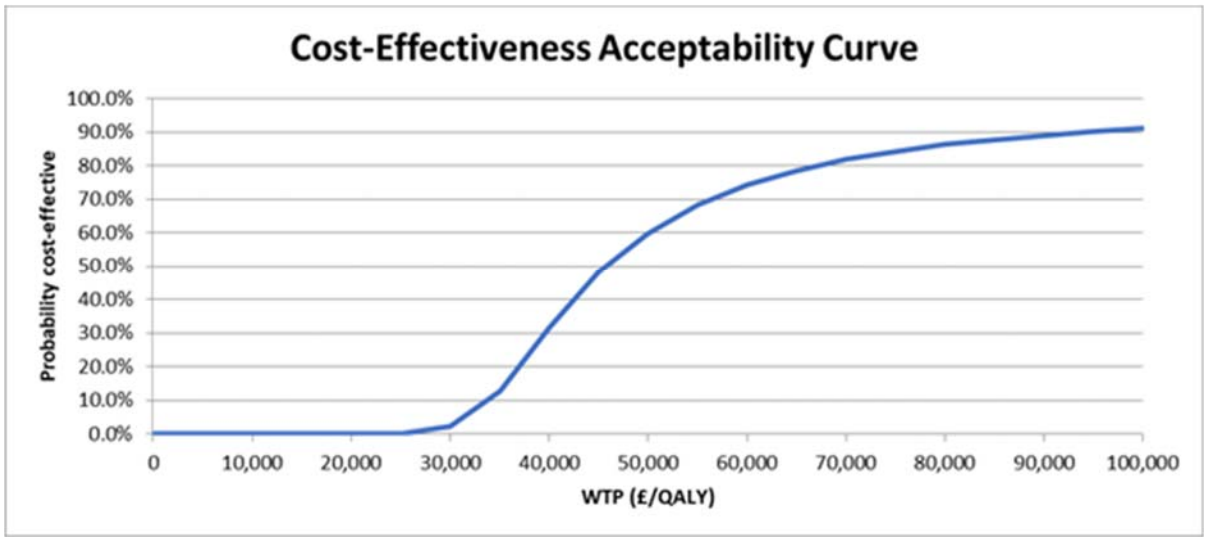
PSA, probabilistic sensitivity analysis; CE, cost-effectiveness

Figure 6 PSA scatter plot: [redacted]



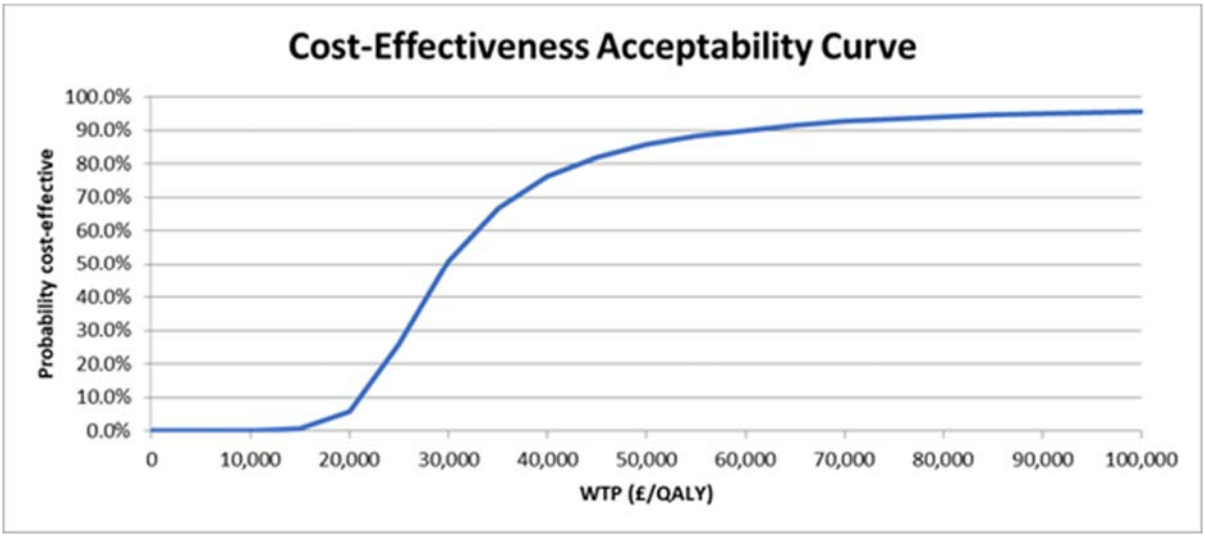
PSA, probabilistic sensitivity analysis.; CE cost-effectiveness

Figure 7 Cost-effectiveness acceptability curve of imlifidase: [redacted]



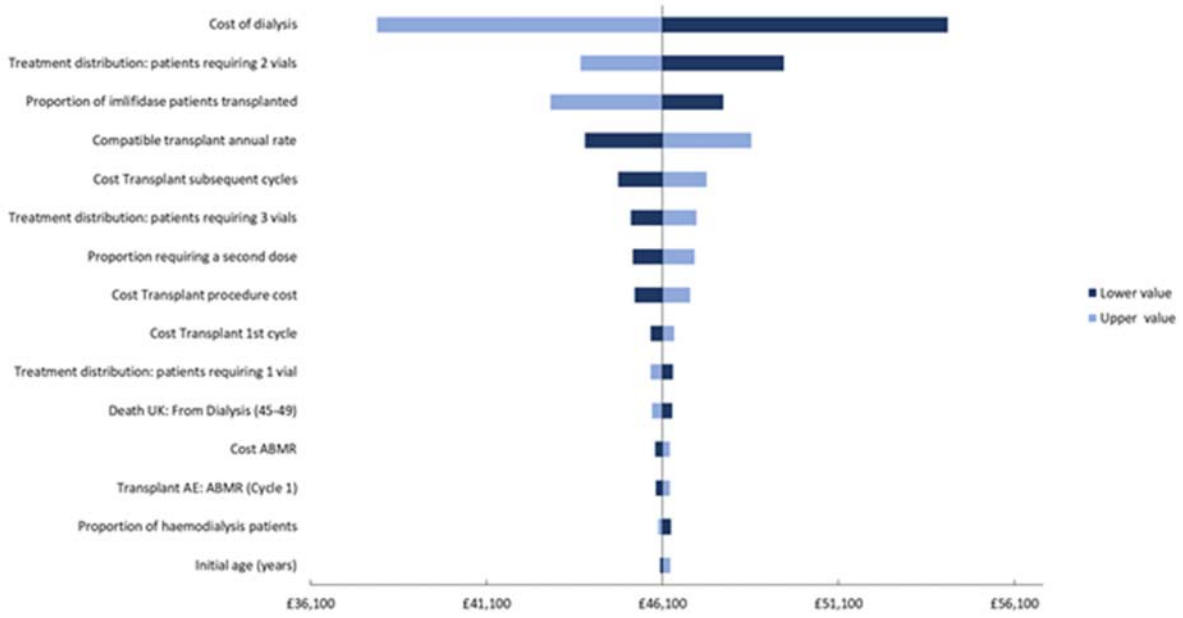
WTP, willingness to pay.

Figure 8 Cost-effectiveness acceptability curve of imlifidase



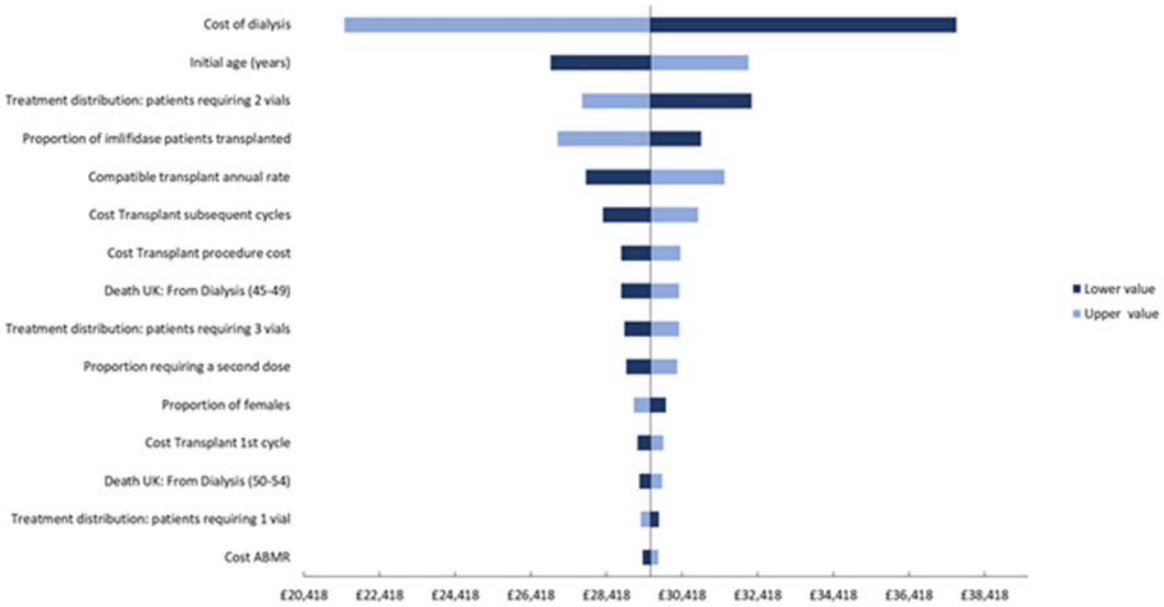
WTP, willingness to pay.

Figure 9 Results of the one-way sensitivity analysis:



AMBR, antibody-mediated rejection.

Figure 10 Results of the one-way sensitivity analysis: [redacted]



AMBR, antibody-mediated rejection.

Table 7 Results of the scenario analyses: [redacted]

	Δ Costs (discounted), £	Δ QALY (discounted),	ICER, £	Difference from baseline, %
Reference Case	[redacted]	[redacted]	46,096	
Scenario 1: Time horizon, 10 years	[redacted]	[redacted]	122,079	165
Scenario 2: Time horizon, 20 years	[redacted]	[redacted]	59,271	29
Scenario 3: Graft loss extrapolations, iBox	[redacted]	[redacted]	52,782	15
Scenario 4: Graft loss extrapolations, All	[redacted]	[redacted]	46,546	1
Scenario 5: Survival extrapolations, UT	[redacted]	[redacted]	80,392	74
Scenario 6: No caregiver disutility			47,591	3

Scenario 7: Caregiver disutility (Nagawasa et al. 2018)	[redacted]	[redacted]	46,965	2

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; UT, unlikely to be transplanted

Table 8 Results of the scenario analyses: [redacted]

	Δ Costs (discounted), £	Δ QALY (discounted),	ICER, £	Difference from baseline, %
Reference Case	[redacted]	[redacted]	29,589	
Scenario 1: Time horizon, 10 years	[redacted]	[redacted]	78,174	164
Scenario 2: Time horizon, 20 years	[redacted]	[redacted]	36,904	25
Scenario 3: Graft loss extrapolations, iBox	[redacted]	[redacted]	34,855	18
Scenario 4: Graft loss extrapolations, All	[redacted]	[redacted]	29,935	1
Scenario 5: Survival extrapolations, UT	[redacted]	[redacted]	48,191	
Scenario 6: No caregiver disutility	[redacted]	[redacted]	30,549	3
Scenario 7: Caregiver disutility (Nagawasa et al. 2018)	[redacted]	[redacted]	30,147	2

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; UT, unlikely to be transplanted

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

A Single Technology Appraisal

ERG Review of Company's Response to Appraisal Committee Meeting 1

Produced by

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Declared competing interests of the authors

Since the publication of the original ERG report, Siân Griffin provided paid consultancy services to Hansa BioPharma AB. These services involved providing clinical expert advice on patient eligibility criteria for imlifidase, and the potential treatment pathway for imlifidase in the NHS.

Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This TE response is linked to ERG report

Farmer C, Knowles E, Kiff F, Long L, Robinson S, Nikram E, Powell R, Moore J, Griffin S, Hatswell A, Crathorne L, Melendez-Torres G.J. Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]. Peninsula Technology Assessment Group (PenTAG), 2020.

1. INTRODUCTION

At the first committee meeting for this appraisal on 11 March 2021, the NICE committee determined that further evidence for the clinical and cost effectiveness of imlifidase was needed before it could reach a decision. On 8 October 2021, the company submitted a response regarding the uncertainties raised by the NICE committee and the Evidence Review Group (ERG). This document provides the ERG's critique of this response.

In sum, the company's response included the following changes:

- Update to the patient eligibility criteria for imlifidase
- Clarification of the expected treatment pathway for imlifidase
- Re-submission of clinical effectiveness estimates from the original trial follow-up
- Provision of '3 year' clinical efficacy data from a follow-up trial of imlifidase (Study-14)
- Challenge to four assumptions incorporated in the ERG model
- Revised model assumptions:
    - Proposed patient population
    - 3 year transplant data
    - iBox graft loss extrapolations
    - ERG assumptions accepted by the company
- Updated patient access scheme (PAS) discount for imlifidase

During its appraisal of the new evidence, the company also responded to clarification queries from the ERG. A brief overview of the key issues raised by the ERG in its original appraisal is provided in Section 0. In Sections 3 and 4, the ERG summarises the new evidence presented by the company, and its view of whether this resolves the uncertainties raised by the ERG and NICE committee during the original appraisal and in Appraisal Committee Meeting 1 (ACM1). The ERG critique of the company's new economic model, incorporating the new PAS discount for imlifidase, is reported in Section 5. Finally, an updated ERG base case is presented in Section 6. Finally, the ERG highlights two additional issues where there is outstanding uncertainty in Section 7.

2. KEY ISSUES RAISED BY THE ERG IN ITS ORIGINAL APPRAISAL

Key Issue 1: Should the appraisal consider the costs and benefits of kidney transplant in those not eligible to have imlifidase?

The ERG raised that, to fully account for costs and benefits given the scarcity of kidneys (with demand exceeding supply and a waiting list), the appropriate analysis should include the costs and benefits forgone of another patient (who may or may not be highly sensitised) receiving the kidney without the use of imlifidase.

Key Issue 2: Are there any potential changes to the treatment pathway and current allocation scheme that need to be considered in decision making?

The ERG considered that the introduction of imlifidase to the treatment pathway may change the positioning of patients within the UK Kidney Offering Scheme (KOS), with a broader impact on the treatment pathway for these and other patients waiting for a kidney transplant.

Furthermore, the ERG noted that the way imlifidase would be used in the treatment pathway, including the use and timing of crossmatch testing and the timing of transplant, was unclear. There was also a lack of clarity about the timing and frequency of donor specific antibody (DSA) testing following transplant. Variations in the delivery of imlifidase could affect clinical outcomes and/or may alter costs.

Key Issue 3: Generalisability of the evidence to NHS contexts

There is uncertainty surrounding the extent that the patients represented by the single arm trials available for imlifidase represent the patients that would receive imlifidase in practice. Only 25 patients in the included trials were considered to be relevant to the decision problem, and as the target population is a new indication, there are no other published data for the demographics and outcomes of these patients. This creates uncertainty about the extent to which the patients in the included trials are representative of the target NHS population, and therefore experienced outcomes consistent with the broader patient population. Moreover, the outcomes of patients in the NHS who match the decision problem cohort and don't receive imlifidase are also unclear.

Key Issue 4: Interpretation of treatment outcomes following transplant

The evidence for imlifidase at the time of its appraisal was restricted to four single-arm studies, comprising a total of 54 patients (25 of whom were considered relevant to the decision problem cohort). Without a matched analysis, it is not possible to determine whether outcomes observed in the studies would have been observed without imlifidase. As stated above, it's also uncertain

what outcomes these patients would typically have without a transplant facilitated by imlifidase, and therefore what values should be used in the comparator arm of the economic model. In particular, the ERG were concerned about whether transplant outcomes seen in the included studies and extrapolated using iBox were representative.

Key Issue 5: Comprehensiveness of the clinical evidence base

The ERG were concerned that the clinical effectiveness evidence presented by the company contained omissions and unclearly reported. Where outcomes were reported, the timing of measurement was often unclear, and continuous data were frequently reported without variance data. This creates significant uncertainty about the efficacy and safety of imlifidase in the target population. In particular, the ERG was concerned with poor reporting of crossmatch conversion data (the primary outcome for the clinical trials) and the type and consequences of AMR episodes.

Key Issue 6: Specifying the comparator arm in the economic model

The company model used a post-hoc scope i.e. given a patient got a transplant, versus remaining on dialysis. This does not match the NICE scope, which compares imlifidase versus clinical management without imlifidase. To account for this, the ERG estimated the number of people in the comparator arm who would receive a transplant without the use of imlifidase. This estimation had a significant impact on the ICER, but was associated with uncertainty due to the lack of data on transplants specific to the decision problem cohort.

Key Issue 7: Source of quality of life data in the economic model

No quality of life data were collected in the company studies, and some data used in the company's economic model were old (i.e. pre-2005). In its base case, the ERG used utility values from a new systematic review published after the CS (Cooper et al. 2020). The ERG also considered additional patient-reported outcome data for patients who received imlifidase and undergone a transplant would be informative.

3. MAJOR CHANGES TO THE CLINICAL EVIDENCE

In this section, the ERG presents a summary of the new clinical evidence presented by the company, and the ERG view on whether this resolved the key uncertainties raised by the NICE committee.

3.1. Refinement of the patient population

In the original submission, the company had defined the patient population as adults with CKD who have a positive crossmatch with a deceased donor kidney and are '*unlikely to receive a transplant'* under the kidney offering scheme (KOS). While the ERG accepted that clinicians may recognise those patients meeting this criteria, a lack of definition over the cohort of patients who are unlikely to receive a kidney in current practice led to uncertainties in best supportive care for these patients. These uncertainties were explored by the ERG in its basecase and scenario analyses, and were found to impact meaningfully on the ICER for imlifidase.

3.1.1. Revised company approach

The company used data provided by NHS Blood and Transplant (NHSBT) and input from clinical experts to update the eligibility criteria for imlifidase. According to the new criteria, patients must have a cRF of ≥99%, a matchability score of 10 and have been on the waiting list for a transplant for at least two years in order to be eligible for imlifidase under the revised company submission. In addition, all delisting strategies must have been explored and the patient must be fit to receive, and fully understand the implications of, a transplant with increased immunological risk. The company suggested that patients will be assessed for eligibility by a multidisciplinary team using 'auditable criteria' to ensure only those unlikely to receive a transplant will be treated with imlifidase. During clarification, the company further refined the eligible population to include only those currently receiving dialysis.

3.1.2. ERG view

The ERG considered that the refined population characteristics presented by the company in their updated submission provide more certainty to the previously ambiguous description of the eligible population. Prior to the change at clarification to require all patients to be receiving dialysis, clinical advice to the ERG was that the new criteria are appropriate and that they reflect those that are least likely to receive a transplant. The ERG were advised that, initially, a subgroup of patients within the new definition may be treated with imlifidase (for example those

with cRF = 100%), and this will be expanded to include the full patient eligibility criteria once centres had gained experience with the treatment pathway pre- and post-transplant. The ERG were also advised that further research and experience with imlifidase may alter clinicians' views on the most appropriate patient group for imlifidase, and this could lead to either a narrowing or broadening of the patient eligibility criteria.[1]

At clarification, the company changed the patient eligibility criteria to specify that, in addition, eligible patients should be receiving dialysis. Prior to this, clinical advice to the ERG was that a small proportion of patients (approximately 5%) who meet the other criteria for imlifidase would not be receiving dialysis after 2 years. This may be because patients were listed pre-emptively ahead of their kidney failing (and thus requiring dialysis), or because after some period of treatment, dialysis had become contra-indicated. The ERG therefore considered the possibility that introducing the requirement for patients to be receiving dialysis would exclude a small number of patients who otherwise meet the eligibility criteria and are therefore unlikely to receive a kidney transplant. As the requirement for dialysis was made at clarification, the ERG were only able to consult briefly with its clinical advisors, who advised that while this would exclude a small proportion of patients, it would otherwise be a reasonable criteria.

Only [redacted] patients in the company's included trials meet the company's updated patient eligibility criteria (including the requirement to be receiving dialysis), and therefore there is uncertainty about the generalisability of the totality of the clinical evidence to other patients meeting these criteria. Furthermore, due to the lack of evidence in the new patient population, the company and ERG economic model includes data from broader patient trial samples for numerous inputs, including clinical outcomes (see breakdown in Table 11, Section 6.1).

3.2. Clarification of the proposed treatment pathway for imlifidase

In its report the ERG raised concerns about a lack of clarity in the proposed treatment pathway for imlifidase. This was considered a significant issue given the importance of minimising the cold ischaemic time (CIT) prior to a kidney transplant, and thus maximising the use of available kidneys. One specific area of uncertainty was around crossmatch testing, as it was not clear to the ERG how many tests would be needed and at what stage they would be carried out.

In addition, the ERG was unclear about how the kidney offering scheme (KOS) would be affected in the UK by the introduction of imlifidase, since this could broaden the pool of donors available to highly sensitised patients. If the KOS remains unchanged, patients therefore

maintain their prioritisation under the KOS despite the reduction of their sensitisation as an obstacle to transplant.

The ERG also raised an uncertainty surrounding DSA testing post-transplant. The company indicated that DSA testing should be in line with existing guidelines for patients who have undergone desensitisation. However, the trial data available were insufficient to estimate the testing that would be required. Clinical advice to the ERG also indicated that more frequent testing may be required.

3.2.1. Revised company approach

In the revised submission, the company set out a more detailed pathway for the use of imlifidase, which was later updated in response to the ERG's clarification questions. To address a lack of clarity around timings in the pathway, the ERG created the treatment pathway shown in Figure 1, which was subsequently accepted by the company at clarification. However the company advise that this treatment pathway may alter over time with experience of imlifidase, and that they will advise NICE where changes to the pathway are indicated.

With regard to crossmatch tests, the company advised that one crossmatch test would be needed prior to infusion with imlifidase, and either one or two crossmatch tests may be needed following infusion (at 2- and 4-hours following treatment). If a positive crossmatch remains, patients will receive another dose of imlifidase followed by another one or two crossmatch tests. At clarification the company stated that up to four crossmatch tests could be required where a second dose is needed, though they also reported that an average of [redacted] crossmatch tests were used for patients in the clinical trials who meet the updated patient eligibility criteria.

In the updated submission, the company maintain that DSA testing will remain equivalent to that used in current practice for patients who have undergone desensitisation.

3.2.2. ERG view

The ERG acknowledges that as a new technology, the treatment pathway for imlifidase may alter with experience, and considered it appropriate that it remains under review by the company and its clinical advisors. However, the ERG notes that alterations to the treatment pathway over time may impact on the clinical outcomes for patients treated with imlifidase. In particular, changes to the pathway that alter the cold ischaemic time (CIT) of the donor kidney may affect the clinical benefits of transplant. This would be most problematic where changes to

the pathway increases CIT, as this may lead to poorer treatment outcomes and an increased risk of wastage of kidneys.

The company's updated submission has not resolved the ERG's concerns about the impact of crossmatch testing on the CIT of donor kidneys. The evidence suggests that the time needed to administer and receive the results of crossmatch tests may take between 10- and 24-hours per patient, depending on: the number of tests required; the time each patient needs to exhibit a crossmatch conversion; and the time it takes centres to receive the results of crossmatch tests. This is on the basis that:

- the results of a crossmatch test may take between four and six hours, depending on centre protocols and availability.
- the company advises that crossmatch tests should be conducted at 2- and 4-hours post-infusion with imlifidase
- trial evidence showed that [redacted] of patients required between 6- and 24-hours following treatment with imlifidase to exhibit a crossmatch conversion (although these data are limited by the timing of tests, as described in Section 3.3.2.1)
- a minority of patients will require a 2nd dose of imlifidase ([redacted]% in trial patients meeting the newly defined patient population)
- the company states that up to 4 crossmatch tests may be needed for a single patient, although evidence presented at clarification showed an average of [redacted] crossmatch tests per patient in the newly defined patient population, implying that some patients may need more than [redacted] tests.
- trial data from the original decision problem cohort presented by the company showed that mean CIT in the trials was [redacted] hours.

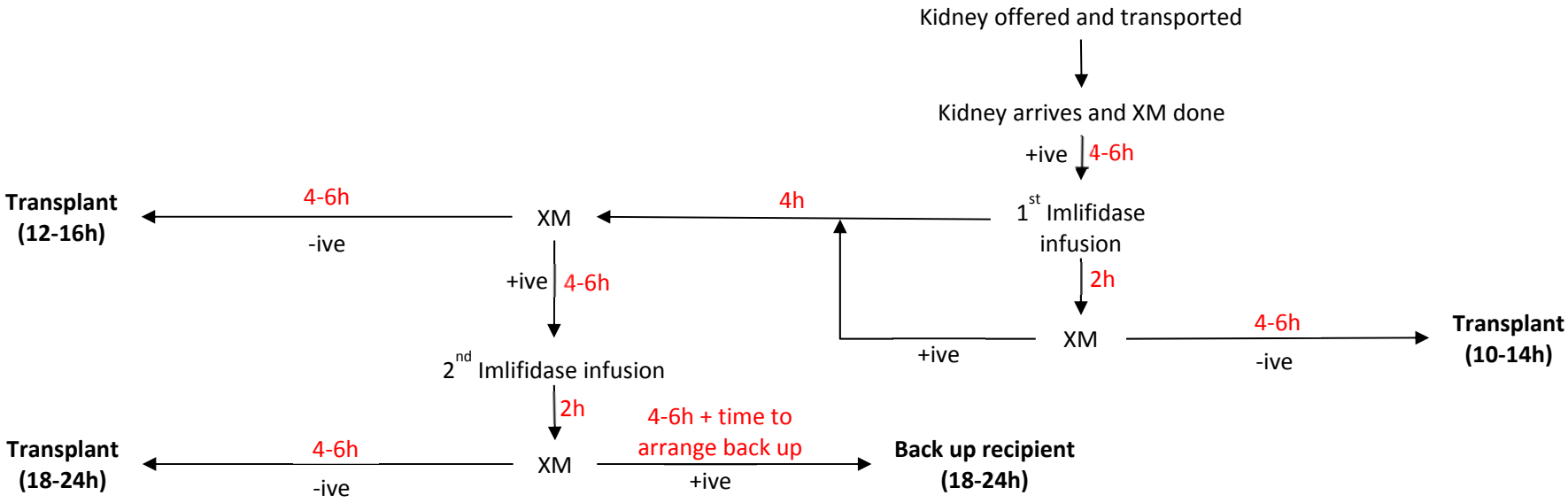
The ERG also understands that the current average CIT in the NHS is 11-12 hours. Pending clinical evidence in an NHS population, the true range of CIT in kidneys received by patients treated with imlifidase is uncertain; however the ERG considered it plausible that a small number of patients treated with imlifidase may receive a donor kidney with a CIT exceeding 24 hours (the threshold advised to the ERG as a cause for concern). As the clinical evidence for imlifidase has a relatively short follow-up duration, the true survival of donor kidneys in patients treated with imlifidase is uncertain, though the ERG consider it possible that these patients may

have poorer treatment outcomes than if they were to receive a kidney transplant without imlifidase. The ERG also considered it possible that there may be an increased risk of wastage of the donor kidney if a crossmatch conversion was not exhibited within an acceptable timeframe.

Clinical advice to the ERG was that the impact of crossmatch testing on CIT may be reduced if clinicians are able to save time in other areas of the treatment pathway, for example to carry out the first crossmatch test prior to the transportation of the kidney using a sample from the donor. Moreover, some centres may choose to arrange a 'backup patient' who could receive the transplant if a patient treated with imlifidase did not exhibit a negative crossmatch within a reasonable timeframe. This may need to be a patient local to the treating centre, and therefore may be outside of typical allocation priorities of the KOS, however this may reduce the risk of wastage of the donor kidney. Clinical advice to the ERG was that reducing CIT was important for ensuring that patients achieve the best possible outcome following treatment, but that some small risk of wastage of the kidney may be acceptable to clinicians, as a small risk of wastage is a currently accepted risk within the KOS. Overall, the ERG considered that CIT would be monitored in reviews of the treatment pathway for imlifidase, but that based on current understanding of the pathway, it is plausible that a small number of patients may experience a long CIT that may negatively impact on their treatment outcomes.

The company's expected DSA testing regimen remains unchanged from the original submission, which stated that testing would be equivalent to that currently used for patients who have undergone desensitisation. As described in the original ERG report, the ERG has received clinical advice that more frequent DSA testing may be required in patients who have undergone desensitisation with imlifidase. The ERG expects that this area of uncertainty may become clear as experience of using imlifidase in practice increases.

Figure 1: Treatment pathway agreed between the ERG and company during clarification



Abbreviations: ERG, evidence review group; h, hours; XM, crossmatch; +ve, positive; -ve, negative

3.3. Reanalysis of trial data

As summarised in Key Issue 5, the ERG were concerned that missing and inconsistent reporting of the reporting of clinical evidence in the CS limited interpretation of the efficacy of imlifidase.

3.3.1. Revised company approach

The company re-submitted further clinical evidence for imlifidase from the trials reported in the original company submission (CS), including variance data missing from some outcomes, and additional outcomes of interest requested by the ERG and NICE committee (where these were measured). At clarification, the ERG requested that the company provide clinical evidence for a number of outcomes in three relevant populations to the company submission: the newly defined patient population; the 'most relevant patient population (to be defined by the company) in the absence of evidence in the new population; and the sample of all patients in the clinical trials who received a dose of imlifidase. The company selected the "unlikely to be transplanted" population as the next most relevant population, using the definition chosen in the clinical trials of imlifidase. A summary of the evidence re-submitted by the company in response to the requests of the ERG is presented in Table 1.

3.3.2. ERG view

The clinical data provided by the company at clarification is presented in Table 1 below. As noted in Section 3.1.2, while the ERG considered the new definition for the patient population to be appropriate, the ERG also noted that only [redacted] patients in the company trials met these criteria. While the size of the sample reflects the small group of patients who clinicians consider to be eligible for imlifidase, it does create uncertainty in the generalisability of clinical outcomes beyond the trial sample. The ERG considered the clinical data presented by the company in its re-submission again lacked clarity, with some data missing or reported in varying formats that made interpreting the data challenging. However, the data provided by the company at clarification was much improved, and (with the exception of infection rates, which are discussed in Section 3.3.2.5) the ERG has no further concerns about the clarity of clinical data available.

3.3.2.1. Crossmatch conversion

The data presented by the company showed that all patients meeting the new eligibility criteria for imlifidase exhibited a crossmatch conversion and received a transplant after treatment with imlifidase. This evidence shows a very high success rate for crossmatch conversion following

treatment with imlifidase in the target population. However, pending further clinical evidence in a large sample of relevant patients, the ERG considered it unlikely that the rate of crossmatch conversion would remain 100% in clinical practice. This is because a small number of patients in the trials did not achieve a crossmatch conversion (n=1, though this person nevertheless proceeded with transplant) or did not receive the full dose of imlifidase due to adverse reactions (n=2). The ERG was unaware of any reason why the rate of conversion/adverse reactions would be different in the new patient population, who are more sensitised than in the broader trial samples. Pending further evidence in a larger sample of the relevant population, the ERG considered it unlikely that the rate of crossmatch conversion would remain at 100% in clinical practice.

The trial data showed that two patients in the new population ([redacted]%) received a 2nd dose of imlifidase prior to crossmatch conversion. As discussed in Section 3.2, the company expects that a small number of patients will require a 2nd dose of imlifidase to exhibit a crossmatch conversion, though given the small patient numbers in the trial, the ERG considered the true proportion of patients needing a 2nd dose is uncertain. The ERG were unclear on whether a 2nd dose is required in patients because one dose is insufficient, or because one dose is insufficient to cause a crossmatch conversion within the required timeframe. The company advises that patients receive a crossmatch test at 2- and 4-hours after treatment, but in the trials the data showed that a sizeable minority of patients exhibited a crossmatch conversion [redacted] after treatment with imlifidase. These patients may therefore show a positive crossmatch at the time of the test, but would have shown a negative crossmatch test some hours later. In this context the ERG was unclear whether the 2nd dose would be necessary to expedite conversion, or would be precautionary (and therefore unnecessary in some instances). The trial data showing the time at which crossmatch conversion occurred was highly limited, as this was measured inconsistently across patients. Therefore, the ERG considered that understanding of the timing of crossmatch conversion, and the subsequent requirements for the timing of crossmatch testing, may alter with further evidence.

3.3.2.2. MFI levels

The company reported mean and median MFI levels in patients with cPRA ≥99% and cPRA 100% before treatment with imlifidase, and at various timepoints following treatment. There is no established threshold to indicate where MFI levels are problematic for transplant or clinical outcomes. In its original report, on advice from clinical advisors, the ERG used a threshold of ≥3000 as a marker of MFI levels that may be a cause for concern; although the ERG noted that

in practice, the absolute size and rapidity of change in MFI levels is more meaningful to clinicians. Clinical advice was that a threshold of ≥1000, used by the company in its new submission to indicate a meaningful change in MFI, was too low.

The new data presented by the company shows that MFI levels drop significantly following treatment with imlifidase. Mean/median MFI levels appear to [redacted] until day 3 following treatment, at which point they begin to rise. Between day 7 and day 14, MFI levels had [redacted]. Variance data reported showed that there was wide variation in the reduction and rebound of MFI levels following treatment across patients. In the original submission, the company reported that [redacted] and [redacted] of patients showed a DSA with an MFI >3000 at two- and 24-hours following treatment with imlifidase, respectively. At clarification, the company reported that [redacted] patients in the newly defined patient population exhibited MFI levels below 3000 at one or more timepoint following treatment with imlifidase, although [redacted] in the 'unlikely to be transplanted' population ([redacted]%) did not experience a drop in MFI below 3000 at any time.

The ERG was uncertain to what extent data on MFI levels are meaningful for determining the clinical effectiveness of imlifidase. While the data showed a significant reduction in MFI levels following treatment, which is consistent with the mechanism of imlifidase, the chaotic measurement of MFI levels in the trials and the lack of an absolute threshold to interpret MFI levels limits the interpretability of these data. While a fast and/or large rebound in MFI levels may indicate an increased risk of rejection, clinical advice to the ERG was that the rate of rejection (or the rate of treatment given for rejection) in the trial samples may be a more reliable outcome. Moreover, clinical advice to the ERG was that MFI levels in the short-term following transplant are not a reliable indicator of long-term graft survival.

3.3.2.3. Transplant rejection

The data presented by the company showed that in the newly defined patient population, [redacted] exhibited antibody-mediated rejection (AMR) and [redacted] exhibited chronic AMR during the original trials. In the same sample, [redacted] received treatment for AMR. The rate of AMR in the new population was higher than reported for either the 'unlikely to be transplanted' ([redacted]%) or 'all imlifidase' ([redacted]%) populations, and thus the trend is for [redacted] risk of rejection in patients who are more sensitised prior to transplant. The company also reported rates of cell-mediated rejection,

though clinical advice to the ERG was that this outcome is less of a cause for concern in sensitised patients, as it is rates of AMR that may affect the long-term survival of the graft.

Clinical advisors to the ERG were concerned by the high rate of rejection in the trials, noting that this is much higher than would be seen amongst patients who are not sensitised (estimated to be approximately 10%). Episodes of rejection can threaten the long-term viability of the transplant, and aggressive treatment for rejection may be needed, which carries its own risks. In those patients with cPRA ≥ 99% and cPRA = 100%, [redacted]%) were resolved by 6 months, and [redacted] AMR episodes resulted in graft loss (this was a patient in the 'all imlifidase' population). However, clinical advisors nevertheless considered that these events may have negative consequences for graft survival, and that clinical evidence with a longer trial follow-up is needed to establish the impact of AMR for patients treated with imlifidase.

3.3.2.4. Graft survival

Median graft survival at 6-months in the newly defined patient population was [redacted], which is comparable with graft survival reported in the other trial populations. As noted in the original ERG report, this rate of graft survival is comparable to a non-sensitised population of patients[2] and is improved compared to other highly sensitised populations[3]. However, advice from clinical experts is that the length of follow-up in the included trials may be too short to show any meaningful differences in graft survival, and advice was that graft survival is likely to be worse than would be expected in non-sensitised patients.

3.3.2.5. Infection

The company has repeatedly declined to report the rate of infection in the decision problem cohort for this appraisal. These data were requested by the ERG during its original appraisal, as well as in the follow-up discussions for the first appraisal committee meeting. In its re-submission, the company again reported the rate of infections in the 'all imlifidase' population, simply noting that rates in the ≥99% cPRA and 100% = cPRA subgroups did not differ "significantly" (thus unclear if this refers to statistical significance, the absence of which may be misleading in such a small sample). At clarification for this re-submission, the ERG again requested the overall rate of infection in the new patient population and/or in the next most relevant population. However, the company again declined to provide this (having deleted this row from the table provided by the ERG). The ERG therefore did not have data for the risk of infection in the new patient population, and was concerned that the company has repeatedly ignored requests to provide this.

The risk of infection is a significant concern for patients who receive a transplant, particularly for those who receive treatment with imlifidase (or any desensitisation regimen). An understanding of the risk of infection is important for understanding the potential clinical and cost implications of treatment with imlifidase, and for patients to make an informed choice about whether to receive treatment with imlifidase. This therefore remains a major, and concerning, omission from the company evidence.

Finally, the ERG raised the possibility that those patients who received 2 doses of imlifidase may be at increased risk of infection. The company did not report the risk of infection in these patients, though again noted that the risk was "not significantly different" (again as only 3 patients in the 'all imlifidase' population received a 2nd dose, any statistical significance would be nearly impossible to achieve). The ERG considered this to also be an area of uncertainty, however noted that this would likely still be the case even if the company had supplied these data, given the small number of patients who received a 2nd dose of imlifidase.

Table 1: New clinical evidence provided by the company at clarification

	Newly defined patient population	**'unlikely to be transplanted'**	**'All imlifidase' population**
Sample size	[redacted]	[redacted]	[redacted]
Overall rate of crossmatch conversion (x/X, %)	[redacted]	[redacted]	[redacted]
Overall rate of crossmatch conversion using FACS (x/X, %)	[redacted]	[redacted]	[redacted]
Number of patients who received 2 doses of imlifidase	[redacted]	[redacted]	[redacted]
Total number of crossmatch tests conducted (only physical XM included, B or T-cell at same time counted as same test, CDC and FC counted as separate tests)	[redacted]	[redacted]	[redacted]
Total number of (FC) crossmatch tests conducted (only FCXM included, B or T-cell at same time	[redacted]	[redacted]	[redacted]

	Newly defined patient population	**'unlikely to be transplanted'**	**'All imlifidase' population**
counted as same test)			
Number of patients who received a transplant after treatment with imlifidase (x/XX, %)	[redacted]	[redacted]	[redacted]
Rate of AMR (x/XX, %), in Original trials	[redacted]	[redacted]	[redacted]
Rate of chronic AMR (x/XX, %), in Original trials	[redacted]	[redacted]	[redacted]
Rate of cell-mediated rejection (x/XX, %), in Original trials	[redacted]	[redacted]	[redacted]
Rejection leading to graft loss (x/XX, %), in Original trials	[redacted]	[redacted]	[redacted]
Number of patients receiving treatment for AMR (x/X, %), in Original trials	[redacted]	[redacted]	[redacted]
Overall survival at final follow-up (x/X, %), in Original trials	[redacted]	[redacted]	[redacted]
Graft survival (median and 95%CI) at 6 months	[redacted]	[redacted]	[redacted]
Survival with functioning graft (median and 95%CI) at 6 months	[redacted]	[redacted]	[redacted]
Patient survival (median and 95%CI) at 6 months	[redacted]	[redacted]	[redacted]
Number of patients whose MFI levels remained above 3000 at all measured timepoints (x/XX, %)	[redacted]	[redacted]	[redacted]
Rate of re-transplant (x/XX, %)	[redacted]	[redacted]	[redacted]

Abbreviations: AMR, antibody-mediated rejection; CDC, complement dependent cytotoxicity; CI, confidence interval; FACS, fluorescence-activated cell sorting; FC, flow cytometry; MFI, mean fluorescence intensity; XM, crossmatch

3.4. Provision of '3 year' trial data

Clinical advisors to the ERG advised that the limited follow-up duration of evidence presented in the CS limited an evaluation of the survival of transplanted kidneys, and the impact of this type of transplant on patients. Studies 02, 03, 04, and 06 were complete at the time the CS was submitted, and involved a follow-up of 64 – 180 days. The company also presented interim data from Study 14, which was an ongoing observational study evaluating efficacy, safety and health-related quality of life (HRQoL) in transplanted patients who had been treated with imlifidase. Evidence from Study 14 in the CS was based on a limited sample available at 2 years. The NICE committee was concerned about the duration of long-term follow-up data for post-transplant outcomes in people treated with imlifidase, and the validity of predictions of graft survival using the iBOX tool. In addition, the NICE committee raised concerns about the high rate of AMR in people treated with imlifidase, and considered that further follow-up data for these patients would be useful for understanding the longer-term benefits and harms of imlifidase.

3.4.1. Revised company approach

The company presented follow-up data for up to 3 years from the ongoing Study 14. Data were available for 39 adult patients with a positive crossmatch who were treated with imlifidase, of whom 13 had cPRA ≥99% and were transplanted with a deceased donor kidney (Kjellman et al. 2021[1]). The company presented data for patient survival, graft survival (death censored), and eGFR (ml/min/1.73m2) separately for subgroups who did and did not exhibit AMR; however, data in a combined sample of these subgroups, and a subgroup of the 13 patients noted above, were reported in the associated trial publication (Kjellman et al. 2021[1]). Baseline characteristics for these patients are reported in Table 2 and outcomes are shown in Table 3 and Figure 2 (reproduced from Kjellman et al. 2021).

At clarification, the company provided data for patients meeting the new eligibility criteria who were enrolled in the follow-up study (n=[redacted]). The publication of the follow-up study noted that there was some attrition over the course of the follow-up period, due to graft loss, mortality, or loss to follow-up. It's unclear how many patients meeting the new eligibility criteria completed follow-up at 3 years, however of the 13 patients with cPRA ≥ 99.9%, who received a deceased donor

transplant, only 6 patients were available at the final 3-year follow-up. Data during follow-up for the new population was restricted to rates of rejection and graft loss, which were presented by the company at clarification (reported in Table 4).

Table 2: Study 14 baseline characteristics and need for dialysis post-transplant

Characteristics	XM+, n = 39	AMR & XM+, n = 15	No AMR & XM+, n = 24	XM+, DD and cPRA ≥ 99.9%, n = 13
Patient age (years); mean (SD)	43.2 (13.0)	44.5 (14.3)	42.3 (12.3)	45.3 (12.6)
Female; n (%)	18 (46%)	6 (40%)	12 (50%)	5 (38%)
Region, US; n (%)	28 (72%)	9 (60%)	19 (79%)	11 (85%)
Race; n (%)				
White	30 (77%)	11 (73%)	19 (79%)	9 (69%)
Black	4 (10%)	2 (13%)	2 (8%)	2 (15%)
Asian	3 (8%)	1 (7%)	2 (8%)	1 (8%)
Other	2 (5%)	1 (7%)	1 (4%)	1 (8%)
Time on dialysis prior to imlifidase transplantation (years); mean (SD)	6.4 (5.6)	7.4 (6.1)	5.9 (5.4)	9.3 (7.2)
Deceased Donor; n (%)	32 (82%)	13 (87%)	19 (79%)	13 (100%)
Total CIT; mean (SD)	21.0 (10.0)	23.8 (11.5)	19 (8.5)	22.7 (9.6)
Re-transplants; n (%)	27 (69%)	10 (67%)	17 (71%)	9 (69%)
cPRA[a] (%); median (1st & 3rd quartile)	99.62 (94.92, 99.96)	99.80 (93.70, 99.99)	99.53 (96.55, 99.91)	99.99 (99.97, 100)
Crossmatch positive; n (%)	39 (100%)	15 (100%)	24 (100%)	13 (100%)
Pre-dose DSA[b] (MFI); median (1st & 3rd quartile)	7791 (4108, 16 320)	13009 (6515, 21 580)	5727 (2699, 9470)	16292 (7133, 21 824)
Pre-transplant DSA[c] (MFI); median (1st & 3rd quartile)	774 (292, 1754)	1584 (904–3303)	576 (193–1387)	1292 (774, 2600)
DGF[d]; n (%)	17 (44%)	7 (47%)	10 (42%)	6 (46%)
DGF duration[e] (days); median (1st & 3rd quartile)	10 (6, 26)	24 (8, 28)	9 (4, 14)	12 (9, 23)

Source: Kjellman et al. 2021[1]

Abbreviations: CIT; cold ischaemic time; cPRA, calculated panel-reactive antibodies; DD, deceased donor; DGF, delayed graft function; DSA; donor specific antibodies; SD; standard deviation; XM+, positive crossmatch

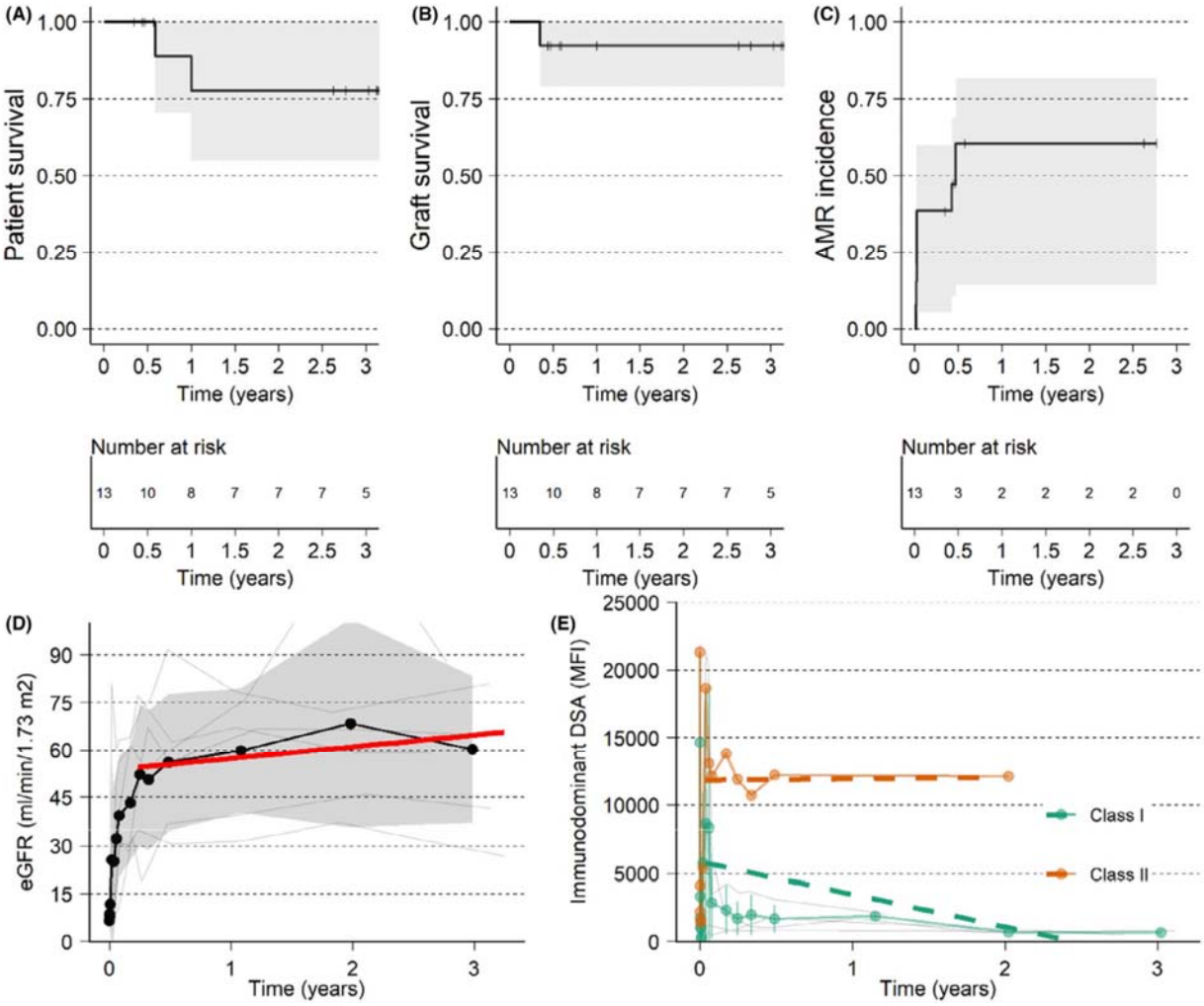
Table 3: Results from the '3-year' follow-up study (Kjellman et al. 2021)[1]

Characteristics	XM+, n = 39	AMR & XM+, n = 15	No AMR & XM+, n = 24	XM+, DD and cPRA ≥ 99.9%, n = 13
Survival				
Death-Censored Allograft Survival at 3 years	84%	93%	77%	92%
Patient Survival at 2 years	90%	85%	94%	NR
Patient Survival at 3 years	90%	85%	94%	NR
AMR				
14 days	NR	NA	NA	5/13 (38%)
1 month	11/39 (28.2%)	NA	NA	NR
6 months	15/39 (38.5%)	NR	NA	7/13 (53.8%)
AMR-mediated graft loss	NR	NR	NR	0%

Source: Kjellman et al. 2021[1]

Abbreviations: AMR, antibody-mediated rejection; cPRA, calculated panel-reactive antibodies; DD, deceased donor; eGFR, estimated glomerular filtration rate, XM+, crossmatch positive

Figure 2: Outcome of the group with XM+, DD, and cPRA ≥ 99.9% (reproduced from Kjellman 2021) [1]



Note: Class I and II refer to HLA class

Abbreviations: cPRA, calculated panel-reactive antibodies; DD, deceased donor; XM+, crossmatch positive

Table 4: Results from the '3-year' follow-up data in the new eligible patient population and the 'unlikely to be transplanted' population

Characteristic	New eligible patient population (n=9)	'Unlikely to be transplanted' population (n=19)
Rate of AMR (x/XX, %), in Follow-up trial	[redacted]	[redacted]
Rate of chronic AMR (x/XX, %)	[redacted]	[redacted]
Rate of CMR (x/XX, %)	[redacted]	[redacted]
Rejection leading to graft loss (x/XX, %)	[redacted]	[redacted]
Number of patients receiving treatment for AMR (x/X, %)	[redacted]	[redacted]
Graft survival (median and 95%CI) at 3 years	[redacted]	[redacted]

Characteristic	New eligible patient population (n=9)	'Unlikely to be transplanted' population (n=19)
Survival with functioning graft (median and 95%CI) at 3 years	[redacted]	[redacted]
Patient survival (median and 95%CI) at 3 years	[redacted]	[redacted]

Abbreviations: AMR, antibody-mediated rejection; CI, confidence interval; CMR; cell-mediated rejection

Source: company's clarification response

3.4.2. ERG view

While the ERG welcomed the provision of data at a longer follow-up, it noted that the quality of the data available beyond the original trials was limited. A very small number of patients who met the new eligible patient population for imlifidase were enrolled in the follow-up (n=[redacted]), and study attrition was high, with only 6/13 (46%) of patients with cPRA ≥ 99.9% who received a deceased donor transplant available at the final 3-year follow-up. Thus the ERG noted that the 3-year timepoint is in reality data up to 3-years, as opposed to the usual terminology which would indicate 3-year minimum, or a median of 3-year follow up. The ERG also noted that very few outcomes were available for these patients, and as noted by the company in their updated submission, there is uncertainty surrounding data for the rebound of antibodies, and for the long-term sustainability of transplants. Overall, the ERG considered that the best evidence for imlifidase remains limited to the initial 6-months following transplant, due to the larger sample size and breadth of available outcome data. Clinical advice to the ERG was that longer-term data (beyond 3-years) is needed to establish clinical outcomes for patients who receive a transplant facilitated by imlifidase, particularly graft survival and HRQoL. A brief comment on the data presented is provided in the following sections.

3.4.2.1. Transplant rejection

[redacted]%) in the new patient population received treatment for AMR, but [redacted] cases of AMR were confirmed during follow-up. In the 'unlikely to be transplanted' population, [redacted]%) received treatment for AMR, and [redacted]%) exhibited AMR. This rejection [redacted] graft loss. [redacted] in either group experienced chronic or cell-mediated rejection. These data suggested to the ERG that the greatest risk of rejection amongst patients treated with imlifidase is in the early months following transplant.

3.4.2.2. Graft survival

Median graft survival at final follow-up was shown to be high in both samples. Clinical advice to the ERG was that they would expect graft survival to drop in subsequent years, and for this to be poorer than graft survival for non-sensitised patients. However, longer follow-up data is needed to establish whether graft survival would be comparable with patients who receive a transplant following other de-sensitisation regimes.

3.4.2.3. Infection

Infection rates were measured in the follow-up study; however, were not reported by the company in their re-submission. As noted in Section 3.3.2.5, the company chose not to provide these data, having deleted this row from the table provided by the ERG when completing their response.

3.4.2.4. Patient survival

Median patient survival at final follow-up was [redacted] in the new eligible patient population ([redacted]%), compared to both the 'unlikely to be transplanted' population ([redacted]%) and the 'all imlifidase' population ([redacted]%). In its original report, the ERG noted that clinical advisors expect a higher rate of mortality in those with greater sensitisation, due to the increased cumulative burden of immunosuppression. However, the lack of a matched comparison with the trial populations prevents drawing conclusions about the extent to which mortality rate may differ from non-sensitised patients who receive a kidney transplant.

3.5. Details on the PAES study

At present, imlifidase has conditional marketing authorisation for use in the UK, pending further evidence for its clinical effectiveness and safety. This data will partly be derived from an additional non-randomised open-label study of imlifidase, which the company refer to as a post-authorisation efficacy and safety (PAES) study. The study will be conducted in sites across Europe, and will have partial overlap with the target population for imlifidase in the NHS. No data is currently available from this study to contribute towards the NICE appraisal of imlifidase.

4. REVISED COMPANY'S ECONOMIC MODEL

The company provided a new economic model to support the additional information submission for imlifidase. The new model appears to have been developed from the original model and not adapted from the ERG version. However, the updated model does not have the ability to reach the original company base case through changing settings. Changes made to the model were briefly listed in the company's additional information submission however, the individual impact on the company's original base case ICER of these changes was not provided.

As a consequence of providing a new economic model, neither the original company nor original ERG base cases could be recovered. Furthermore, the company have not provided an explicit description of all changes to the economic model between the original and updated models submitted to NICE or presented the individual impact upon the originally submitted ICER with each change. The totality of changes implemented to go from the company's original ICER to the updated ICER is not transparent, therefore the ERG was unable to fully validate how the updated ICER has been achieved when starting from the originally submitted base case.

4.1. Revised company approach

The following changes to the company model were highlighted in the company's additional information submission.

4.1.1. Utility source

The original company base case used utility values obtained from Liem et al (2008), a meta-analysis of values of patients with and without transplant. In addition to being outdated, this approach was limited as the patients who do, and do not receive transplant are likely to differ, which led the ERG to identify longitudinal sources detailing the impact of transplant within individuals.

The NICE committee felt the estimates from Li et al. (2017) and Cooper et al. (2020) (ERG base case) were more appropriate utility sources than the Liem et al paper. Li et al. was felt to better reflect clinical practice as the values are UK specific, while Cooper et al. was a more recent study.

The company chose to adopt the estimates from Li et al. in their base case, reasoning that the values better reflect UK specific clinical practice.

ERG view

The ERG found the use of Li et al. to inform utilities in the company's revised base case to be an acceptable assumption. For confirmation, the ERG approached Dr Li who was happy to discuss the study and confirmed that she believes the study to be valid and relevant, for which the ERG would like to place their thanks on record. Dr Li identified one limitation of the study, which is that utilities were derived using the EQ-5D-5L value set, as it was performed prior to the 'crosswalk' being preferred.

The availability of a literature study does not resolve the issue that no data on the quality of life of patients treated with imlifidase exists (nor more generally the quality of life of highly sensitised patients). It does however give an acceptable proxy for use in modelling.

4.1.2. Proportion of imlifidase patients to receive a transplant

The ERG and NICE committee felt there was uncertainty in the rate of crossmatch conversion from positive to negative and that the 100% of patients receiving a transplant following imlifidase treatment in the company's original submission was unrealistic. The ERG adjusted the proportion of imlifidase patients to receive a transplant by accounting for the two patients who did not receive the full dose (due to adverse reactions, resulting in no subsequent transplant), resulting in a rate of transplant for the imlifidase arm of 96.3%. A further one patient failed to achieve a negative FACS crossmatch with imlifidase however, went on to receive a transplant as a negative virtual crossmatch result was achieved and clinical judgement supported the procedure.

For this reason, the ERG explored adjusting the transplantation rate for the intervention arm for this additional patient in a scenario analysis, resulting in a 94.4% rate of transplantation. The NICE committee's preferred assumptions included either 96.3% or 94.4% to be used as the proportion of patients who received a subsequent transplant following imlifidase to reflect the outcome of the trials.

The company opted to change their proportion of imlifidase patients to receive a transplant following treatment from 100% to 96.3% in their updated submission.

ERG view

The ERG agreed with the revised company base case assumption that 96.3% of imlifidase patients receive a transplant following treatment. However, the ERG considered this proportion

to be uncertain as the true rate of crossmatch conversion is unknown, especially considering there was an additional patient who received imlifidase but did not achieve a negative FACS crossmatch. Therefore, the ERG has explored a range of alternative proportions in the scenario analyses, including the 94.4% rate of transplantation when the patient who received a negative FACS crossmatch (but went on to receive a subsequent transplant) was included in the calculations. Furthermore, there remains uncertainty around the appropriate value, given the limited patient numbers that have been studied to date.

4.1.3. Dialysis status distribution source

The company used data from the UKRR 21st Annual report to inform the proportion of patients assigned to haemodialysis and peritoneal dialysis in the original model. The ERG requested and received data from NHSBT on the treatments received by highly sensitised patients (cRF ≥99%) on the transplant waiting list and noted that the model comparator should allow a proportion of patients to receive no dialysis to align with current practice (as seen in the NHSBT data). The ERG used the data provided by NHSBT to inform the proportion of patients receiving haemodialysis, peritoneal dialysis and those not currently on any dialysis treatment for the comparator arm.

The company opted to use the distribution of dialysis from the NHSBT data however, adjusted the proportions so that all patients are receiving dialysis. The company's initial justification for assigning all comparator patients to dialysis was; "it is estimated that the proportion of patients in Tier A and on the waiting list for ≥2 years who are not on dialysis is very small or zero". Following clarification, the company narrowed the eligible population down to only those who are already receiving dialysis (discussed in Section 3.2).

ERG view

The ERG agreed with the company's use of the NHSBT data to inform the distribution of treatments received by highly sensitised patients (cRF ≥99%), but noted concerns with adjusting the proportions so that all comparator patients are receiving dialysis.

The population criteria presented in the company's additional information submission excluded the requirement of patients to have been treated with dialysis for ≥2 years. The company

engaged with clinical experts to determine a suitable eligibility criteria for patients who should receive imlifidase which resulted in the following:

- cRF ≥99%
- Matchability score 10
- On the KOS waiting list for ≥2 years

The ERG then presented these criteria to clinical experts and received input confirming this was a suitable population definition for imlifidase. The additional requirement of dialysis treatment for ≥2 years was not mentioned by the company in the initially proposed population for imlifidase and was only added following questions to the company from the ERG. It is therefore unclear to the ERG whether the additional criterion (dialysis ≥2 years) had been validated by clinical experts to the company. The ERG was able to briefly discuss the validity of this change in population with its own clinical experts over email, where it was indicated that the inclusion of this additional criteria is reasonable, though they expected a small proportion of patients to be on the waiting list without having received dialysis at ≥2 years.

When considering the eligibility criteria, prior to the 'receiving dialysis for ≥2 years' element added at clarification, the ERG agreed with the company that the proportion of patients not requiring dialysis in the population is likely to be small however, considered it highly unlikely that this proportion is zero. The ERG sought clinical opinion on the proportion of patients who were estimated to meet the company's new population criteria, prior to the inclusion of 'patients currently receiving dialysis' (cRF ≥99%, matchability score 10, on the KOS waiting list for ≥2 years): three clinicians independently stated that 5% was a reasonable assumption for the proportion of patients meeting the company's criteria but not receiving dialysis (two estimated 5%, one estimated 5-10%). The clinicians stated that though it is relatively unusual for patients on the KOS waiting list for over 2 years to not need dialysis, there are a small proportion of patients for whom that is true. The justification was that some patients are added to the KOS waiting list pre-emptively, prior to kidney failure (and thus prior to dialysis treatment) and also that kidney function can plateau at a low level, therefore the patient is on the waiting list but has not required dialysis to that point.

In the revised economic model, the company provided the option to apply the ERG's original assumption regarding dialysis distribution (use of NHSBT data including 'not on dialysis' for the initial 2 years, followed by all patients assigned dialysis for all subsequent years). Selecting this

option in the model allowed patients who experience a graft failure in the initial 2 years to be assigned to no dialysis. Though it is anticipated that a graft failure (in either the imlifidase or SoC populations) would result in dialysis treatment, the impact on the ICER is likely to be negligible.

The ERG considered the inclusion of the criteria 'patients receiving dialysis for ≥2 years' to be unrealistic in that it would mean patients meeting all other criteria (cRF ≥99%, matchability score 10, on the KOS waiting list for ≥2 years) would be denied imlifidase treatment despite otherwise being unable to receive a transplant through lack of a compatible kidney. In addition, it is unclear whether the requirement of dialysis treatment for ≥2 years had been validated by clinical opinion to the company. Due to the introduction of this criteria at a late point in the ERG review period, the ERG was only briefly able to validate the inclusion with its own experts, without the opportunity to discuss any potential implications.

The ERG anticipated that imlifidase treatment may be provided to those rare patients who have a stable but low level of kidney function (estimated by clinicians to be ~5%), despite a patient not receiving dialysis for 2 years or more. To impose a dialysis rule on such patients would place clinicians in a difficult ethical position, in needing to give unnecessary medical treatment (dialysis) in the long-term interest of the patient (i.e., to gain access to imlifidase, and thus, transplant).

Therefore, the ERG base case allows for 5% of dialysis patients at the model start to not be receiving dialysis treatment, with all patients assumed to be on dialysis from 2 years onwards.

4.1.4. Caregiver disutility source and application

The original company base case used a Japanese reference to calculate caregiver disutility and applied it to 100% of haemodialysis patients. The ERG questioned the calculations based on the number of sources and assumptions used and instead identified a disutility from a study of informal carers' quality of life (Thomas et al. 2015[7]). The ERG anticipated that not all haemodialysis patients would have a caregiver and so applied this disutility to 90% of patients, exploring applying to 100% of haemodialysis patients in a scenario analysis.

The company's updated base case incorporated the disutility from Thomas et al. and applied the disutility to 90% of patients to align with the ERG's preferred assumptions.

ERG view

The ERG agreed with the changes made to the caregiver disutility source and application to align with the original ERG preferred assumptions.

4.1.5. Haemodialysis travel cost

In the original company submission the company included ambulance transport as an NHS-incurred cost for patient travel for haemodialysis with a cost which appeared more in line with an emergency ambulance (£219). The ERG anticipated that in reality this would be a shared community ambulance and in the absence of suitable cost data, redistributed the 18% of haemodialysis patients from ambulance to the other NHS-incurred travel costs. This approach seems to also have been preferred by the NICE committee.

The company's updated base case aligns with the ERG's and committee's preferred approach and excludes ambulance transportation from the distribution of NHS-incurred transport.

ERG view

The ERG agreed with the changes made to haemodialysis travel costs.

4.1.6. Inclusion of crossmatch test costs

No costs associated with crossmatch testing were included in the original company base case. Given that a negative crossmatch is required following imlifidase infusion, the ERG felt it was inappropriate to exclude these costs from the analysis. Therefore, the ERG applied the cost of one FACS crossmatch test (£300) following each administration of imlifidase received.

The company's updated analysis applies the cost of one crossmatch test following each full dose of imlifidase.

ERG view

The company's updated analysis applied the cost of one crossmatch test following each full dose of imlifidase, per the ERG's original base case. Following the company's additional information submission, the ERG requested the total number of crossmatch tests received by patients in the new company defined population (cRF ≥99%, matchability score 10, on the KOS waiting list for ≥2 years [also termed 'new post-hoc' analysis]), 'unlikely to be transplanted' and

'all imlifidase' populations. The company response is provided in **Error! Reference source not found.**.

Table 5: Number of crossmatch tests from the imlifidase trials

	New post-hoc (new company defined population)	"Unlikely to be transplanted" population	'All imlifidase' population
Sample size	[redacted]	[redacted]	[redacted]
Number of patients who received 2 doses of imlifidase	[redacted]	[redacted]	[redacted]
Total number of crossmatch tests conducted (only physical XM included, B or T-cell at same time counted as same test, CDC and FC counted as separate tests)	[redacted]	[redacted]	[redacted]
Total number of (FC) crossmatch tests conducted (only FCXM included, B or T-cell at same time counted as same test)	[redacted]	[redacted]	[redacted]

Abbreviations: CDC, complement-dependent cytotoxicity; FC, flow cytometric ; FCXM, flow cytometric crossmatch; XM, crossmatch.

The data provided by the company suggested that, at the very least, a mean of [redacted] FACs crossmatch tests per subject can be expected for imlifidase patients. Given that [redacted] of the 46 'all imlifidase' patients received a second dose, an average of [redacted] tests were given per full dose ([redacted] [number of tests divided by the number of doses]). The ERG anticipated that at least one crossmatch test would be administered prior to a usual transplant, and therefore expected that an additional [redacted] tests at least are required for patients treated with imlifidase. However, this could range up to an additional [redacted] tests ([redacted] minus one test administered prior to usual transplant) based on the data from the imlifidase trials.

In light of the new crossmatch test data, the ERG have revised their preferred assumptions regarding the number of crossmatch tests applied for patients in the imlifidase population, increasing from 1 to [redacted], discussed further in Section 6.1.

4.1.7. Inclusion of DSA test costs

No costs associated with donor-specific antibody (DSA) testing were applied within the original model. Clinical opinion to the ERG stated that DSA testing would be implemented, as a minimum, when a graft failure is expected however, may be used more regularly to check for antigens. At the original clarification stage the company provided the cost for a DSA test on one antigen (£55) and stated clinical opinion was that on average three antigens of interest could be expected however, this could range between one and six antigens. The ERGs approach applied the cost for three tests for use in transplant maintenance (testing for three antigens, once annually) and at the time of graft failure.

The company's updated analysis applies the cost of three DSA tests to transplant maintenance (testing for three antigens, annually) and the cost of three DSA tests at graft failure to align with the ERG preferred assumptions.

ERG view

The ERG agreed with the changes made to account for DSA testing to align with the original ERG preferred assumptions.

4.1.8. Average patient weight

The original submission sourced average patient weight from a 2009 Welsh study (75kg). The ERG preferred the use of the average weight from the clinical trials ([redacted]kg) to inform the costing of imlifidase.

The company's updated analysis applies the average patient weight from the clinical trials.

ERG view

The ERG agreed with the changes made to average patient weight to align with the original ERG preferred assumptions.

4.1.9. Population used to predict graft survival

In the original company base case, graft survival data was taken from the iBox predictions, extrapolated using a Weibull distribution. As the iBox predictions were developed based on a general transplant population, as opposed to a highly sensitised population, the committee considered the iBox projection and extrapolation to be too optimistic, particularly at 20 years.

The ERG felt the iBox projections were preferable to the clinical trial data options (due to short-term follow up). However, the ERG were concerned about the difference in the proportion of patients with a previous transplant between the population considered in the appraisal and the iBox population (60% versus 15%, respectively). In addition, clinical opinion indicated that those with a first transplant would be expected to have improved graft survival over those with a subsequent transplant. Therefore, the ERG agreed with the company that graft survival should be informed by the iBox prediction in the absence of better long-term data however, performed a scenario analyses where a 0.90 hazard ratio (HR) was applied to the curve to explore the effect on the ICER should the iBox predictions prove optimistic for the population considered in this appraisal. The committee suggested that longer-term graft survival data from the imlifidase trials could be presented, as well as real-world (NHS) graft survival data to aid decision making.

Data on outcomes up to 3-years post-transplant from the clinical trials has been published. The company's updated analysis uses the newly published follow up data in the 'unlikely to be transplanted' population to inform graft loss, extrapolated with an exponential distribution.

ERG view

Though the company updated the model with outcome data up to 3 years post-transplant from the clinical studies, the ERG considered the data too immature to provide good estimates of graft survival due to the high level of uncertainty for imlifidase-infused patients in the long term. The key concerns from the ERG and committee regarding graft survival were that the iBox projections and subsequent extrapolations were potentially too optimistic (particularly in the longer-term) for the population considered in this submission. Clinical opinion also expected graft survival in patients treated with imlifidase may not be as successful as in a non-sensitised population.

The company's revised base case used the new data in the 'unlikely to be transplanted' population, extrapolated with an exponential distribution, to inform graft survival. Table 6 presents the 5-, 10- and 20-year graft survival predictions available in the model, where the iBox is seen to predict the lowest survival at both time points. Given the concerns from the ERG and committee were that the iBox estimates of graft survival may be too optimistic, the company's revised base case does not address these concerns. Furthermore, the updated assumptions from the company estimate better survival than in the original submission. As the company's base case used data with very little long-term follow up (n=6 at 3-years), the ERG did not find

the use of the 'unlikely to be transplanted' population to inform graft survival a reasonable assumption.

Table 6: Graft survival predictions

	iBox predictions, with Weibull extrapolation (Original company base case)	Unlikely to be transplanted, with exponential extrapolation (revised company base case)	All imlifidase, with exponential extrapolation
5-year survival	[redacted]	[redacted]	[redacted]
10-year survival	[redacted]	[redacted]	[redacted]
20-year survival	[redacted]	[redacted]	[redacted]

Figure 3 presents the extrapolated graft survival of the three options within the economic model. At all time points (post time = 0) the iBox model is observed to predict reduced survival compared to the trial data.

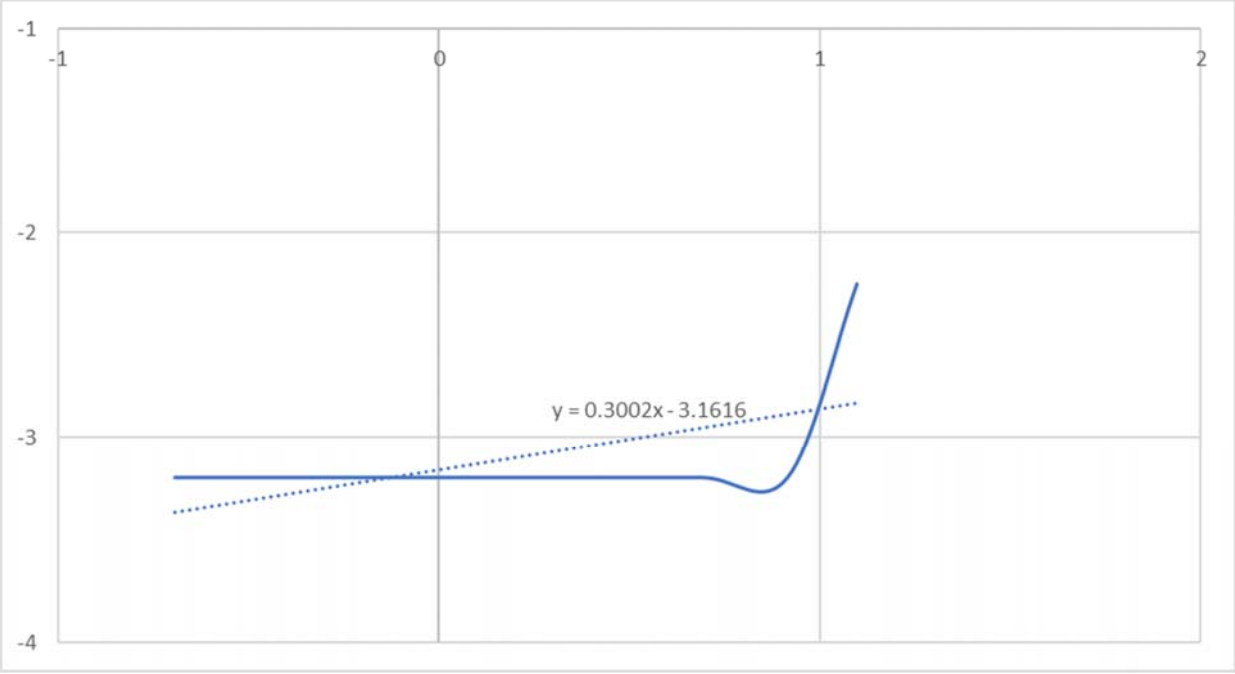
Figure 3: Graft survival extrapolations to 20 years

Abbreviations: UTT, unlikely to be transplanted

Beyond this fundamental limitation, the ERG also disagreed with the choice of an exponential distribution (which implies a constant failure rate) to extrapolate the imlifidase trial data. Though

the optimal model based on statistical goodness-of-fit, it is known that the risk of graft failure is highest in the period immediately following transplant with this risk reducing over time thus, not constant. The ERG requested hazard function plots of both the 'graft survival' and 'overall survival with a functioning graft' outcomes in order to assess the shape of the hazard function to aid in making an informed decision on the most appropriate curve extrapolation for the data. The company did not provide the plots due to tight timelines, however did offer to provide post-meeting if still required. As the ERG were able to produce log-cumulative hazard plots from the data within the model to assess the hazards, the request was not followed up however, the ERG note that provision of the plots in the original submission would be useful for decision making. Figure 4 presents the log-cumulative hazard plot of the 'unlikely to be transplanted' graft survival data. The trend of the curve is not constant, indicating that neither an exponential nor Weibull model would be appropriate to extrapolate the data. Furthermore, the gradient of the curve is less than 1, indicating an exponential model is unlikely to be suitable.

Figure 4: Log-cumulative hazard plot – Unlikely to be transplanted graft survival



Given the scarcity of data available, it is unlikely that any parametric extrapolation would be able to produce a reasonable long-term estimate of the data. Thus, clinical opinion was sought by the ERG, with one clinician estimating 30-40% graft survival at 10 years with imlifidase treatment (in the highly sensitised population) and approximately 60-70% at 10 years in a non-sensitised population. At 20 years, clinical opinion estimated 30-40% graft survival for non-sensitised

patients and <30% in the imlifidase treated population, noting there is a paucity of data relating to 20-year graft survival. Two other clinicians were approached but stated it would be too difficult to estimate long-term graft survival with imlifidase. A clinical expert highlighted a paper by Manook et al. (2017)[8] providing 1- and 5- year graft survival estimates for HLA incompatible living donor transplants and matched patients with a compatible deceased donor in the UK, summarised in Table 7. The clinician stated that graft survival for an incompatible HLA transplant from a deceased donor would be expected to be inferior compared to a living donor, as is receiving an incompatible transplant compared to a compatible transplant. Given that the 5-year estimates for all three model options are greater than the 5-year survival for an incompatible HLA living donor transplant (76%, 82%, 83% versus 68%) and the estimates from the imlifidase data are greater than the 5-year survival for a compatible deceased donor transplant (82%, 83% versus 77%), the ERG considered the graft survival options in the model to be overly optimistic. Furthermore, clinical opinion stated that survival for the imlifidase population should best be predicted using data from incompatible, rather than compatible transplants.

Table 7: Graft survival - Manook et al.[8]

	Living donor HLA incompatible transplant	Deceased donor compatible transplant
1-year survival	[redacted]	[redacted]
5-year survival	[redacted]	[redacted]

Abbreviations: HLA, human leucocyte antigens

For patients in a highly sensitised population who achieved a transplant without requiring desensitisation therapy, the data from Manook et al. shows improved survival over an incompatible transplant, aligned with the clinicians who felt that graft survival would be comparable to the non-highly sensitised population. However, the clinicians noted that some patients may never receive a transplant without the aid of desensitisation therapy.

For these reasons, the ERG was concerned that the graft survival estimated in the model was unrealistically optimistic for the imlifidase arm. Furthermore, if transplantation without desensitisation therapy results in better graft survival outcomes than when desensitisation therapy is used, then the patients receiving a transplant in the SoC arm would be expected to have improved graft survival over the imlifidase arm, which is a potential limitation of the model.

As there are limited data to inform a difference between graft survival in a those treated with/without desensitisation therapy in a highly sensitised population, the ERG assumed graft survival to be equal between the imlifidase and SoC arms, but this is a potential limitation. As the graft survival estimates are likely too optimistic, the ERG opted to use the iBox predictions in the ERG base case, with the aforementioned 0.9 HR, noting that these are assumptions due to the lack of medium- and long-term data. Alternative assumptions regarding the HR were explored in scenario analyses.

4.1.10. Update to costs sources

The company's new economic model was updated with the 2021 NHS reference costs.

ERG view

The ERG agreed with the updated costs in the economic model using the 2021 NHS reference costs. The ERG noted that the imlifidase-specific comedication (prophylactic antibiotics) unit costs were obtained from eMIT 2018 and that updated eMIT costs were available however, the impact on the results was likely negligible.

4.1.11. Imlifidase PAS discount

In the original submission the company suggested a simple PAS discount of [redacted]. In the updated analysis the company revised this simple PAS discount to [redacted]**ERG view**

The ERG had no comments on the change to the imlifidase PAS discount.

4.2. Additional outstanding issues

In addition to the changes to the company model discussed in Section 4.1, the ERG identified three other areas of considerable uncertainty in the economic model, detailed as follows.

4.2.1. Proportion of patients to receive a second dose of imlifidase

In the original company submission the company stated "The model assumes that 6.5% of patients will require a second infusion of negative crossmatch is not achieved (based on the proportion requiring a second dose within the clinical trial data)". At clarification the company provided the number of patients who received 2 doses of imlifidase for each population, reproduced in Table 8 below.

The ERG noted that the proportion in the 'all imlifidase' population is incorrect: [redacted] gives [redacted]%, not the [redacted]% presented in the company's Table 2 (company response to ERG questions). Furthermore, the proportion used in the model ([redacted]%) does not appear in the table.

Table 8: Number of patients to receive a second dose of imlifidase

	New post-hoc (new company defined population)	"Unlikely to be transplanted" population	'All imlifidase' population
Sample size	[redacted]	[redacted]	[redacted]
Number of patients who received 2 doses of imlifidase	[redacted]	[redacted]	[redacted]

In light of this information, the ERG considered assigning [redacted]% to a second dose of imlifidase to be an underestimation of the real proportion of second doses received in the imlifidase trials given that the proportions in all three populations was greater than [redacted]%. As a result, the ERG was unclear how the [redacted]% value was achieved. Therefore, the ERG assigned [redacted]% of imlifidase patients to receive two doses of imlifidase (to align with the 'all imlifidase' population) with alternative proportions explored in sensitivity analysis.

4.2.2. Overall survival with a functioning graft

The ERG considered the use of the imlifidase trial data to inform overall survival (OS) with a functioning graft to be a source of great uncertainty in the cost-effectiveness results. As with the graft survival data, the OS data were also too immature to produce reasonable long-term estimates to be used for modelling a lifetime horizon in the population considered for this submission.

The company used an extrapolation of the 'all imlifidase' data to inform OS with a functioning graft, while using an extrapolation of the 'unlikely to be transplanted' population to inform graft survival. Clinical opinion to the ERG indicated that overall survival may be comparable between patients treated with imlifidase, however with a lack of long-term data with imlifidase this remains an area of uncertainty. Due to the lack of long-term imlifidase data, OS with a functioning graft (and graft survival) would ideally have been informed by data in the highly-sensitised population, with information obtained from either the literature (if any such publications exist), or real-world (NHS) data. The extrapolations from the imlifidase trials could then have been validated against the external estimates and a decision on the most appropriate survival estimates could have been made.

The ERG considered that in the absence of better data, either extrapolation from the 'all imlifidase' or 'unlikely to be transplanted' populations could inform OS with a functioning graft. The ERG accepted the company's assumption to use the 'all imlifidase' extrapolations to inform OS with a functioning graft in the base case however, emphasises this is a key limitation of the company's submission and argued that much better data could have been used to inform this in the model. In addition, as there was little reason to select the 'all imlifidase' extrapolations over the 'unlikely to be transplanted' (and the 'unlikely to be transplanted' population was used to inform graft survival in the company's base case), the ERG explored using the 'unlikely to be transplanted' OS data in a scenario analysis.

4.2.3. Subsequent transplant

A further source of uncertainty was the frequency of a subsequent transplant following graft failure in the population under consideration. A subsequent transplant was not considered within the model however, it was the ERG's understanding that some patients would be able to be re-transplanted. As imlifidase treatment can only be used once to facilitate a transplant in a patient, any subsequent transplants would be performed without desensitisation therapy however, the costs and efficacy associated with a re-transplant were not considered within the economic model. While no patient from the imlifidase trial had received a subsequent transplant by the (up to) 3-year data presented by the company in response to clarification, the data were immature and thus it cannot be assumed that no re-transplantations will occur in the future.

5. REVISED COMPANY COST-EFFECTIVENESS RESULTS

5.1. Company's base case results

Results of the company's base case analysis are presented as an ICER for imlifidase with transplant compared to dialysis (original base case) and SoC (revised base case). Total and incremental costs, QALYs and life years (LYs) are presented for the original base case in CS Table 54 (Document B, p. 155) and the company's response to ERG questions for the revised base case, replicated in Table 9. [redacted] patient access schemes (PASs) of [redacted] and [redacted] were applied to the acquisition cost of imlifidase in the original and revised company base cases, respectively. Table 9: Original and revised company base case deterministic results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Original company base case (deterministic) – [redacted] PAS discount							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*30,641*
Revised company base case (deterministic) – [redacted] PAS discount							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case (deterministic) – [redacted] PAS discount							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year; SoC, standard of care.

The company reported a revised base case ICER of [redacted] for imlifidase versus SoC, based on incremental costs of [redacted] and a QALY gain of [redacted]. The revised base case analysis projected [redacted] discounted LYs for patients treated with imlifidase who go on to receive a transplant, of which [redacted] were gained in the 'functioning graft' health state.

5.2. Company's sensitivity analysis

The ERG previously noted discrepancies between the distributions stated and the distributions actually used to vary the parameters in the company's economic model. The company amended the proportion of haemodialysis patients to be varied by a beta distribution as stated (previously a normal distribution was used) however, the cost of kidney transplant procedure and maintenance remained varied by a normal distribution as opposed to the stated 'gamma'

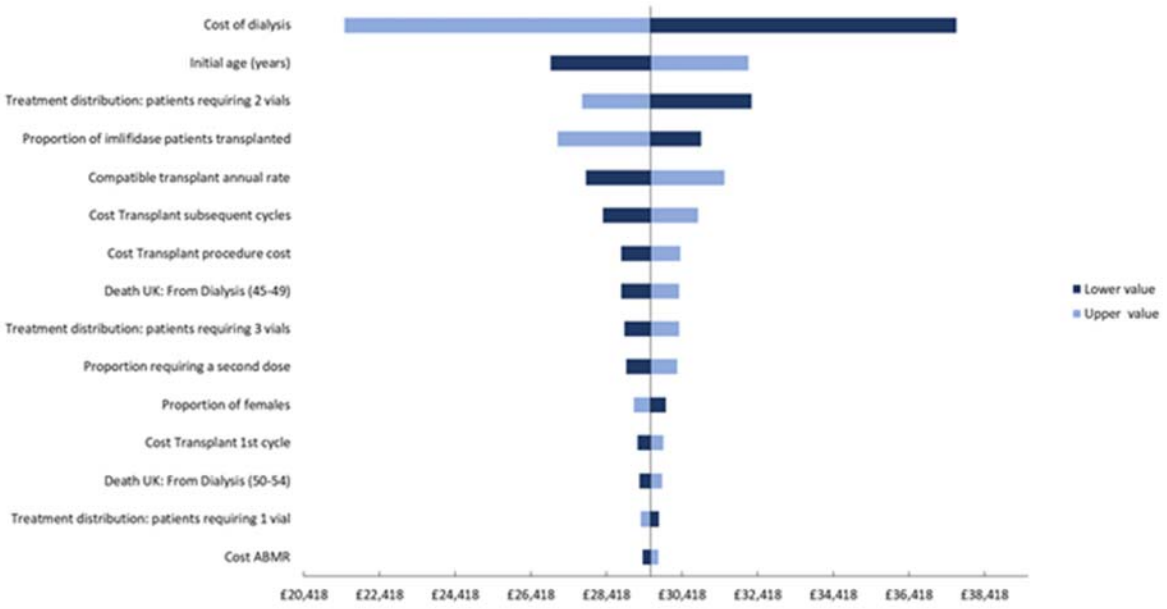
distribution. Furthermore, no adjustments were made to the standard errors (SEs) of the imlifidase AEs, which could have been accurately predicted using the beta distribution rather than using the assumed value. However, the impact of these discrepancies on the sensitivity analysis results were likely negligible.

Following clarification, the company provided one-way sensitivity analysis (OWSA), probabilistic sensitivity analysis (PSA) and scenario analysis results, discussed in turn below.

5.2.1. Company's one-way sensitivity analysis

A tornado plot was used to present the OWSA results (company response to ERG questions; Figure 5), with the ICER as the outcome of interest. The plot showed the results were most sensitive to the cost of dialysis, initial age, proportion of patients requiring 2 vials of imlifidase for a single dose (based on patient weight), the proportion of imlifidase patients transplanted and the compatible transplant annual rate (applied in the SoC arm). Despite these being the main parameters to which the model was sensitive, changes in any of 10 individual parameters could increase the ICER over £30,000, whereas no parameter change (of those parameters included) could reduce the ICER below £20,000. In addition, the proportion of patients requiring 1, 2 and 3 vials should not have been included in the OWSA as these are not independent parameters.

Figure 5: Company's OWSA Tornado plot – [redacted]



Abbreviations: ABMR, antibody-mediated rejection

5.2.2. Company's probabilistic sensitivity analysis

In the company's response to ERG questions, the company provided results of a probabilistic sensitivity analysis (PSA) to explore the impact of parameter uncertainty, based on each model parameters' respective distribution. 10,000 iterations were used within the PSA. The ERG previously noted that graft survival was not included in the PSA, meaning the results underestimated the uncertainty in the decision problem. The ERG noted that graft survival was still not included in the company's revised PSA.

The PSA results were summarised in the company response to ERG questions in a results table (company's Table 6, recreated here in Table 10), cost-effectiveness plane and cost-effectiveness aceptability curve (CEAC). The ERG noted that the results in the company's response to ERG questions were incorrect (company Table 6): both the base case and mean PSA results were the same as those presented in the original company base case therefore, the ERG re-ran the PSA using the company's revised base case (including a [redacted] PAS discount).

The company's probabilistic base case ICER is similar to the deterministic result ([redacted]), though the results do not represent the true full uncertainty in the decision problem as graft survival was not included in the PSA.

Table 10: Revised company mean PSA results (company presented, ERG corrected) – [redacted]

Arm	Totals		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Company presented probabilistic base case					
Imlifidase	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG corrected company probabilistic base case*					
Imlifidase	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year.

Notes:

* ERG re-run of the PSA using the company's base case assumptions

When the ERG ran the PSA using the company revised base case, at a willingness-to-pay threshold of £30,000 per QALY gained, the probability of imlifidase being cost-effective versus

SoC was 51.4%. However, as previously mentioned, these results do not account for any uncertainty around graft survival extrapolation.

5.2.3. Company's scenario analysis

The company provided seven scenario analyses at clarification (company's response to ERG questions).

All scenarios resulted in an increase to the ICER, with only one scenario remaining below £30,000 (graft loss extrapolation informed by 'all imlifidase'). The most notable increases were when a 10-year time horizon was assumed and when changing the overall survival with a functioning graft data source from 'all imlifidase' to the more-closely aligned target population 'unlikely to be transplanted', with ICERs of [redacted] and [redacted], respectively.

The scenario analyses presented were limited in number, with none exploring the impact of model selection on survival extrapolation, or the impact of an alternative dialysis overall survival approach. The scenario analysis results did however, highlight that all alternative assumptions result in an increased ICER and the influence of the data used to extrapolate overall survival with a functioning graft upon the cost-effectiveness results.

6. ERG'S PREFERRED ASSUMPTIONS

In the company's revised submission, several of the ERG's original preferred were accepted, with others addressed through clarification of the patient population (e.g., proportion of the target population receiving dialysis treatment at model start).

6.1. Differences from the (revised) company submission

The ERG's preferred base case assumptions differed from the company's revised base case, with the changes summarised below:

1. The ERG considered the inclusion of the criteria 'patients receiving dialysis for ≥2 years' to be unrealistic in that it would mean patients meeting all other criteria (cRF ≥99%, matchability score 10, on the KOS waiting list for ≥2 years) would be denied imlifidase treatment despite otherwise being unable to receive a transplant through lack of a compatible kidney. The ERG anticipated that imlifidase treatment may be provided to those rare patients who have a stable but low level of kidney function (estimated by clinicians to be ~5%), despite a patient not receiving dialysis for 2 years or more. To impose a dialysis rule on such patients would place clinicians in a difficult ethical position - in needing to give unnecessary medical treatment (dialysis) in the long-term interest of the patient (i.e., to gain access to imlifidase, and thus, transplant). As such, the ERG allowed 5% of dialysis patients at the model start to not be receiving dialysis treatment, with all patients assumed to be on dialysis from 2 years onwards.
2. Following clarification, the company provided the number of crossmatch tests received in the imlifidase trials. In light of this new information, the ERG has increased the number of crossmatch tests applied to the imlifidase arm from 1 to [redacted] in the ERG base case.
3. The ERG considered the 'unlikely to be transplanted' data to inform graft survival to be too immature to produce reasonable long-term estimates and likely too optimistic. Following similar concerns from the committee and in the absence of improved data, the ERG used the iBox predictive model to inform graft survival and applied a 0.9 hazard ratio (HR) as a naïve approach to address these concerns. Though, the ERG noted that this approach was limited due to the lack of available data on the intervention at even intermediate timepoints (i.e., 3 – 5 years), and lack of provision of survival data from a comparable cohort without imlifidase treatment; i.e., highly sensitised patients.

4. Data provided to the ERG at clarification indicated that the [redacted]% of patients receiving a second dose of imlifidase in the model was an underestimation of the true proportion. Given that [redacted]% of the 'all imlifidase' patients received a second dose, the ERG assigned [redacted]% of patients in the imlifidase arm to receive a second dose of imlifidase.
5. In the company's revised model all SoC patients begin on dialysis and can only move to transplant at cycle 1; however, patients in the imlifidase arm who receive a transplant begin the model in the transplant health state. The ERG considered the approach should align between treatment arms therefore, allowed a proportion of SoC patients to begin in the transplant health state at cycle 0 (as per the imlifidase arm) in the ERG's preferred base case.

In addition to the company's scenario analyses, the ERG conducted the following exploratory analyses:

- The ERG considered the use of Li *et al*[4] utilities in the base case to be a reasonable assumption; however, the estimates from Cooper *et al.*[5] also provided a reasonable source for utility values and so were explored in sensitivity analysis.
- The ERG considered the proportion of imlifidase patients going on to receive a transplant to be uncertain, therefore varied this proportion in sensitivity analysis to explore the impact upon the ICER. Of note, 94.4% was implemented as this proportion accounts for the two patients who could not receive the full dose of imlifidase due to AEs and the patient who did not achieve a negative crossmatch however, went on to receive a transplant regardless.
- The ERG considered the proportion of patients receiving a transplant in the SoC arm (annual compatible transplantation rate) to be a source of uncertainty and so varied this proportion in sensitivity analysis to explore the impact on the ICER.
- Following data provided by the company at clarification, the ERG were unclear on the true number of crossmatch tests required during imlifidase treatment. Therefore, this number was varied in sensitivity analysis.
- Clinical opinion to the company stated that between one and six antigens may be of interest for DSA testing. Therefore, the ERG varied the number of DSA tests applied to transplant maintenance and at the time of graft loss in sensitivity analysis.

- The ERG's revised base case applied a HR to the iBox predictions to inform graft survival in an attempt to produce more realistic estimates in the absence of accurate long-term data in the population. The ERG considered this approach limited, and so varied the HR applied in sensitivity analysis to explore the impact of graft survival assumptions on the ICER.
- The ERG considered the proportion of patients to receive a second dose of imlifidase to be a source of uncertainty in the model. Therefore, alternative proportions of [redacted]%, [redacted]% and [redacted]% were explored in sensitivity analysis: [redacted]% represented the ERG's best guess of the proportion who received a second dose in the safety set ([redacted]) however, as the number of patients who required a second dose in the safety set was not presented by the company (and thus is unknown to the ERG), this proportion was considered a lower bound as it is possible that more than [redacted] patients required a second dose. The [redacted]% and [redacted]% are from the 'unlikely to be transplanted' and 'new post-hoc' populations.
- The ERG considered the use of imlifidase trial data to inform OS with a functioning graft to be a source of great uncertainty in the cost-effectiveness estimates. As with the graft survival data, the OS data were too immature to produce reasonable long-term estimates. In the absence of better data, the ERG accepted the company's assumption of using 'all imlifidase' to inform overall survival with a functioning graft. However, given the considerable uncertainty for the long term emphasise this is a limited analysis. The ERG noted there is no strong argument to use the 'all imlifidase' data over the 'unlikely to be transplanted' data therefore, the ERG explored using the 'unlikely to be transplanted' OS with a functioning graft data in a scenario analysis.
- The ERG applied an increased cost of £21,000 for a transplant to account for organ retrieval and transportation (discussed in ERG report, Section 6.2.10).
- The ERG explored the impact of using ERA-EDTA data to inform OS for patients receiving dialysis treatment (UKRR data used in company and ERG base cases).
- The ERG explored applying HRs to the "unlikely to be transplanted" graft survival data used in the company base case to investigate the change in efficacy of graft survival that would cause the company's base case ICER to increase above £30,000, and thus no longer making imlifidase a cost effective option.

For completeness, the ERG presents the model input data sources in Table 11.

Table 11: Model input sources - Company and ERG revised base cases

	Company base case	**ERG base case**
Proportion of patients requiring 1, 2 or 3 vials for 1 full dose of imlifidase	Baseline patient weight – Total safety set (n=54)	Baseline patient weight - Total safety set (n=54)
Proportion of patients requiring a second dose of imlifidase	Total safety set (n=54) – [redacted]%	All imlifidase data (n=46) – [redacted]% *Scenario analysis: [redacted]% - ERG best guess at safety set proportion, [redacted]% - unlikely to be transplanted data, [redacted]% - new post hoc data.*
Proportion of imlifidase to get a transplant	Total safety set (n=54). 96.3% - 52 of 54 patients administered imlifidase who went on to receive a transplant	Total safety set (n=54). 96.3% - 52 out of 54 patients administered imlifidase who went on to receive a transplant. *Scenario analysis: 94.4% - 51 out of 54 patients who achieved a negative crossmatch following imlifidase*
Graft survival	Unlikely to be transplanted data (n=25) - Extrapolated with an exponential distribution *Scenario analysis: iBox predictions- Extrapolated with a Weibull distribution* *Scenario analysis: All imlifidase data (n=46) - Extrapolated with an exponential distribution*	iBox predictions - Extrapolated with a Weibull distribution and a 0.9 hazard ratio *Scenario analysis: iBox predictions - Extrapolated with a Weibull distribution and 0.8, 0.85 and 0.95 hazard ratios* *Scenario analysis: All imlifidase data (n=46) - Extrapolated with an exponential distribution* *Scenario analysis: Unlikely to be transplanted data (n=25) - Extrapolated with an exponential distribution*
OS with a functioning graft	All imlifidase data (n=46) - Extrapolated with an exponential distribution *Scenario analysis: Unlikely to be transplanted data (n=25) - Extrapolated with an exponential distribution*	All imlifidase data (n=46) - Extrapolated with an exponential distribution *Scenario analysis: Unlikely to be transplanted data (n=25) - Extrapolated with an exponential distribution*
OS on dialysis	UK renal registry data	UK renal registry data *Scenario analysis: ERA-EDTA data*
Utilities	Li et al.	Li et al,

	Company base case	**ERG base case**
		Scenario analysis: Cooper et al.
Dialysis distribution	NHSBT data – redistributed to exclude patients not receiving dialysis	NHSBT data – 5% of patients on dialysis for the initial 2 years *Scenario analysis: NHSBT data with 0% and 10% of patients on dialysis for the initial 2 years*
Comparator annual transplant rate	NHSBT data	NHSBT data *Scenario analysis: 5%, 10% and 15% annual transplantation rates*
Number of crossmatch tests following a full dose of imlifidase	Assumption	[redacted] – All imlifidase data (n=46) – number of FCXM tests minus 1 (expected to be given prior to imlifidase treatment) *Scenario analysis: 1 (assumption)* *Scenario analysis: [redacted] – All imlifidase data (n=46) - number of physical FCXM tests minus 1 (expected to be given prior to imlifidase treatment)*

Abbreviations: FCXM, flow cytometry crossmatch; OS, overall survival

6.2. ERG base case results

The ERG determined a set of preferred settings and assumptions that were believed to represent a more plausible estimate of the cost-effectiveness of imlifidase. However, the ERG emphasises that several preferred assumptions such as graft survival estimates and the proportion of imlifidase patients who are likely to receive a transplant without imlifidase remain uncertain.

The ERG's preferred model settings and assumptions are summarised in Table 12. The individual and cumulative impact of each setting on the estimated ICER is presented alongside each change. The results presented are aligned with the base case results provided by the company, including equivalent settings.

Table 12: ERG's preferred model assumptions – [redacted]

Preferred assumption	Section in ERG response to company's revised submission	Individual change to corrected ICER £/QALY	Cumulative ICER £/QALY
Company base case	*Section 5.1*	-	[redacted]
Allow 5% of SoC to receive 'no dialysis'	*Section 4.1.3 & 6.1*	[redacted]	[redacted]
Increase number of crossmatch tests to 2.4	*Section 4.1.6 & 6.1*	[redacted]	[redacted]
Use iBox predictions to inform graft survival with a 0.9 HR	*Section 4.1.9 & 6.1*	[redacted]	[redacted]
Increase proportion of imlifidase patients to receive a second dose to 8.7%	*Section 4.2.1 & 6.1*	[redacted]	[redacted]
Allow SoC patients to begin the model in the transplant health state	*Section 6.1*	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; SoC, standard of care.

A comparison of the revised company's base case analysis and the revised ERG's preferred analysis results are presented in Table 13. The equivalent results of PSA using the ERG preferred assumptions are also provided.

Table 13: Comparison of company and ERG results - [redacted]

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG corrected company probabilistic base case*							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
ERG base case (probabilistic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year

Notes: It was not possible to obtain PSA LY results from the cost-effectiveness model.

* ERG re-run of the PSA using the company's base case assumptions

6.3. ERG sensitivity analyses

A comparison of the company's and ERGs scenario analyses using the ERG's preferred assumptions versus the company's base case is provided in Table 14.

The majority of changes result in an increase to both the company's and ERG's base case results, particularly changes relating to graft survival. Of interest, only a [redacted] HR is required to be applied to graft survival in the company's base case (using the "unlikely to be transplanted" data) to increase the ICER above £30,000. This is particularly important to note as, although it is associated with a high level of uncertainty, graft survival was not included in the PSA and, as seen in Table 14, slight variations of graft survival estimates are impactful on the cost-effectiveness results.

Table 14: Comparison of company and ERG scenario analysis results - [redacted]

Scenario	ICER (£/QALY)	
	Company	ERG
Base case	[redacted]	[redacted]
Company scenario analyses		
Time horizon – 10 years	[redacted]	[redacted]
Time horizon – 20 years	[redacted]	[redacted]
Graft loss extrapolation – iBox*	[redacted]	[redacted]
Graft loss extrapolation – All imlifidase patients	[redacted]	[redacted]
OS with a functioning graft – 'Unlikely to be transplanted' patients	[redacted]	[redacted]
No caregiver disutility	[redacted]	[redacted]
Caregiver disutility source – Nagawasa *et al* (2018)[6]	[redacted]	[redacted]
ERG scenario analyses		

Scenario	ICER (£/QALY)	
	Company	ERG
Utility source – Cooper *et al* (2020)[5]	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 94.4%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 90%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 99%	[redacted]	[redacted]
SoC annual compatible transplant rate – 5%	[redacted]	[redacted]
SoC annual compatible transplant rate – 10%	[redacted]	[redacted]
SoC annual compatible transplant rate – 15%	[redacted]	[redacted]
SoC proportion on 'no dialysis' – 0%	[redacted]	[redacted]
SoC proportion on 'no dialysis' – 10%	[redacted]	[redacted]
Number of crossmatch tests following a full dose of imlifidase - 1	[redacted]	[redacted]
Number of crossmatch tests following a full dose of imlifidase – 5	[redacted]	[redacted]
Number of DSA tests - 1	[redacted]	[redacted]
Number of DSA tests - 6	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.80	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.85	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.95	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Apply alternative transplant cost - £21,000	[redacted]	[redacted]
Change OS dialysis source – ERA-EDTA	[redacted]	[redacted]
Apply HR to "Unlikely to be transplanted" graft survival – 0.9 **	[redacted]	[redacted]
Apply HR to "Unlikely to be transplanted" graft survival – 0.98 **	[redacted]	[redacted]

Abbreviations: ERA-EDTA, European Renal Association – European Dialysis Transplant Association; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life-year.

Note: * iBox data to inform graft survival is applied with no HR in this scenario.

** "Unlikely to be transplanted" data is used to inform graft survival in these scenarios.

7. OUTSTANDING ISSUES

This section highlights issues outstanding, outside the parameterisation of the economic model.

7.1. Scope of the appraisal; patient, or healthcare system

This key issue (key issue 1 for the ERG) remains, though was not pursued by the NICE committee. Namely that the counterfactual (likely better) outcomes that could be achieved by the use of a donor kidney in the wider transplant population are not explored, and this opportunity costs excluded from the calculations presented.

The ERG therefore noted this as an issue of perspective that remains. The work presented therefore takes the decision point to be whether to give imlifidase in the context of individual highly sensitised patients; and does not include the counterfactual outcomes that could have been obtained by the [scarce] kidney in a non-sensitised patient – which would require a population level model.

7.2. Lack of quality of life data measured in the relevant patient population

Although there exist good quality values in the literature on the impact of transplant which may be used as a surrogate, it should be highlighted that there exist no data in this patient population, as they were not collected as a part of the imlifidase study program.

As a part of their evidence submission and clarification thereof, the company provided further data on the planned PAES trial, which will collect data on [redacted], however this will not report for some time, and will still only provide data at limited time points for small patient numbers.

8. REFERENCES

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 20 December 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Chronological list of NICE/NICE committee and NHSE interactions regarding appraisal uncertainties

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report does not mention any of the successful interactions which have taken place since the committee meeting between Hansa Biopharma and NICE, NHSE&I, NHSBT and appropriate clinical experts to help minimise or resolve the uncertainties raised after the first appraisal committee meeting. Pg3	Include. Following the March 2021 appraisal committee meeting, the following correspondence and meetings took place between key stakeholders to resolve the remaining uncertainties - 15/4/21 – NICE committee sends letter to Hansa summarising key issues identified by the committee in order for us to understand its preferred assumptions - 07/05/21 – Hansa letter update to NICE committee - June – August 2021 – Hansa engage throughout this period with NICE Managed Access, NICE Appraisal project team NHSBT (Matthew Robb) and NHSE&I to ensure the scheduling of a NHSE&I hybrid commercial/clinical surgery. Hansa were proactive in working with NICE and NHSE&I to ensure the scope of the surgery was appropriate and valuable for the multi-stakeholder group to discuss the identified uncertainties	The ERG's report should reflect the numerous positive interactions Hansa undertook with NICE and NHSE&I, NHSBT and appropriate external clinicians between the first appraisal committee meeting and now, as that has provided the opportunity for stakeholders to align on steps to minimise or resolve uncertainties for this appraisal. Throughout this process Hansa have provided extensive additional input, in many instances with the support of expert clinicians, which we believe have significantly reduced the uncertainties described in NICE's initial letter post-committee in April 2021. The report should reflect this.	Not a factual inaccuracy. The ERG recognise the constructive nature of many of the meetings Hansa have held, however have tried to present as short a summary as possible, reflecting the evidence as it stands. The ERG would also note that it was not present in the majority of the meetings mentioned, and thus is unable to comment. The appropriate place for these meetings and process to be documented would be in the company submission.

	- 12/08/21 – NHSE&I hybrid commercial/clinical surgery takes place with representation from NICE, NHSE&I and Hansa to discuss uncertainties - 08/10/01 – Hansa letter response to NICE committee on remaining uncertainties identified by NICE Committee - 16/11/21 – Hansa receive ERG clarification questions - 22/11/21 – Hansa response to ERG questions - 23/11/21 – Hansa call with ERG and NICE Appraisal project team to discuss clarification questions. no outstanding issues were raised.		

Issue 2 Patients not currently receiving dialysis to be included into imlifidase patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG wish to include patients who have not previously received dialysis into the eligible patient pool for imlifidase Page 5-7, 26-28, 43, 47-48, 50	Hansa accept the ERG recommendation to include patients who have not previously received dialysis into the eligible patient pool for imlifidase.	Hansa accept the ERG recommendation to include patients who have not previously received dialysis into the eligible patient pool for imlifidase. However clinical feedback suggested a proportion lower than the ERG's proposed 5% should be investigated further. Key findings from calls with 3 experts (Dr Rommel Ravanan, Dr Adnan Sharif and Prof.	The ERG recognise that there is uncertainty around this figure, however would not wish to amend the value given by 3 clinicians independently. The ERG also note that even if the 5% is an overestimate (when it may even be an underestimate), this would be ameliorated by the fact that patients

		Nithya Krishnan, all speaking to us in a personal capacity) in w/c 10 January. 40-50% of patients are waitlisted pre-emptively, However, it is unusual for a patient not on dialysis to remain on the waiting list for considerably longer than 6 months. Only approximately 3% of all adult Deceased Donor (DD) transplantations are pre-emptive (take place prior to dialysis being required). Pre-emptive listing should only occur once a patient reaches an eGFR of less than 15 mL/min/1.73m^2, would be expected to be alive in five years and to be either on dialysis or starting dialysis within 6 months of joining the waiting list. This represents less than 5% of patients waitlisted. An estimate provided by 1 clinician was 2-3%, another 2 clinicians said less than 5%, one of these commented that 5% felt very optimistic. The clinicians engaged do not think that being on dialysis is a requirement for receiving a transplant from an equity point of view.	are all assumed to discontinue at 2 years; which both limits the impact, and potentially overestimates the volume of dialysis received (as some rare patients would likely remain dialysis free).

Issue 3 Scope of the Appraisal

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG believes that the	Remove as an Outstanding	As stated in Section 7.1 of the ERG report:	This is not a factual inaccuracy. The

NICE committee need to re-consider the inclusion of the costs and benefits of kidney transplant in those not eligible to have imlifidase • Pg 3, 51	Issue	*This key issue (key issue 1 for the ERG) remains, though was not pursued by the NICE committee.* We do not consider this an outstanding uncertainty for the NICE committee on the basis that it was not listed as an outstanding uncertainty in the letter sent from the NICE committee to Hansa in April 2021. Kidney allocation always includes a trade-off between equality of access and optimal expected outcomes. The Kidney Offering Scheme (KOS) already takes into account the risk of increasing equity at the expense of some utility in the creation of the highly sensitised priority programme. Imlifidase follows these same principles and enables access to transplant to a small subset of highly sensitized patients who are currently severely disadvantaged as they are unable to benefit from the KOS and therefore have no realistic prospect of a kidney transplant. Kidney transplant is widely accepted as the standard of care for patients with ESRD with improved survival and quality of life benefits.	ERG has appraised new evidence presented by the company in its re-submission, and in its response (a) outlines the key issues raised by the ERG in its original appraisal (p.3) and (b) provides an overview of the issues it considers are outstanding following submission of the new evidence (p.51). The ERG are distinct from the committee, and serve a different purpose in the NICE process. In this instance we note to the committee that this trade-off exists (as do the company) – but that how this is handled is for committee discussion and decision making. We would not wish to pre-empt what the committee would decide.

Issue 4 Quality of Life Evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states the lack of quality-of-life data measured in the relevant patient population is an outstanding issue for the committee • Pg 5, 25, 51	Remove as an Outstanding Issue	Hansa acknowledges that QoL data from imlifidase trials will be collected in our long-term follow up studies including the planned Post Approval Efficacy Study. However, Hansa agrees with the ERG: - in section 7.1: *there exist good quality values in the literature on the impact of transplant which may be used as a surrogate* - in section 4.1: *The availability of a literature study does not resolve the issue that no data on the quality of life of patients treated with imlifidase exists (nor more generally the quality of life of highly sensitised patients). It does however give an acceptable proxy for use in modelling.*	Not a factual inaccuracy. The lack of quality-of-life data taken from patients treated with imlifidase remains a limitation of the data package. That there is data collection planned (note: not ongoing) is noted, however this is not currently available to inform this submission. This is especially problematic as the patients whom Hansa wishes to treat are likely further down the treatment pathway than many, and so existing values may not be applicable (despite being taken from good quality studies). This therefore remains a structural uncertainty.

Issue 5 How KOS affected by introduction of imlifidase

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG queried the process in which the KOS will prioritise	In addition, the ERG was unclear about how the kidney offering scheme (KOS) would	Hansa recommend that this topic is a broader topic than the remit of this imlifidase appraisal. It requires a broader discussion	This is not a factual inaccuracy. The ERG further note that this issue was discussed in more detail in the original

highly sensitised patients. Pg 7	be affected in the UK by the introduction of imlifidase, since this could broaden the pool of donors available to highly sensitised patients. If the KOS remains unchanged, patients therefore maintain their prioritisation under the KOS despite the reduction of their sensitisation as an obstacle to transplant. *This topic is a broader topic than the remit of this appraisal*	with the Kidney Advisory Group and clinical experts on how highly sensitised patients in general are allocated a kidney within the current Kidney Offering Scheme. In terms of the prioritisation status, it will remain unchanged, imlifidase facilitates the conduct of an incompatible kidney transplant that otherwise would not be possible.	ERG report.

Issue 6 Rate of Infections

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The company has repeatedly declined to report the rate of infection in the decision problem cohort for this appraisal." "At clarification for this re-submission, the ERG again requested the overall rate of infection in the new patient population and/or in the next most relevant population. However, the company again declined to provide this (having deleted this row from the table provided by the ERG). The ERG therefore did not have data for the risk of infection in the new patient population and was concerned that the company has repeatedly ignored requests to provide this." Pg 15	Remove sentences which suggest Hansa have repeatedly declined to report the rate of infection.	Hansa strongly denies that it has repeatedly declined to report the rate of infection to the ERG. Even the ERG stated in Section 3.2.2 "However, the data provided by the company at clarification was much improved, and (with the exception of infection rates, which are discussed in Section **Error! Reference source not found.**) the ERG has no further concerns about the clarity of clinical data available." Hansa has provided the clinical study reports for the imlifidase trials for complete transparency and in the October 2021 written response, summarised the infection rates detailed in the SmPC. No difference was seen in the transplanted patients who received a 2nd dose of 0.25mg/kg (data limited to 3 patients) and those receiving one dose Additionally in the Jordan 2020 et al[1] paper for the Study 06 study: *There were no infections considered serious and related to imlifidase. Infections considered probably*	This is not a factual inaccuracy. Throughout the appraisal of imlifidase, the ERG have repeatedly asked the company to provide comprehensive clinical data in their target populations, including the rate of infections. The ERG stated that the company has repeatedly declined to report the rate of infection in the target patient group on the basis of the following: • During its original appraisal of the company submission the ERG requested infection rate data in the target population during clarification, but the company chose not to present these. • Following the submission of the ERG report, the company had the opportunity to re-submit its clinical data to address the concerns raised by the ERG. However, during technical engagement the company elected not to re-submit any

		related to imlifidase but not serious include 1 urinary tract infection. Thirty-one other infections were reported in 14 patients over the course of the 6-mo study as not serious and not related to imlifidase. All infectious pathogens were unspecified, and there were no signals to delineate differences between viral, fungal, or bacterial infections. In addition, the Kjellman 2021 et al[2] paper for the 3-year imlifidase trial data states: *The incidence and pattern (including infectious agent) of serious or severe infections were not different from those observed in kidney-transplanted patients in general and included mainly upper respiratory and urinary tract infections (n= 15).* A temporary reduction of Beta Cell Receptor (BCR)-dependent differentiation of antigen-specific memory B cells into plasma cells or long-lived plasma cells might be expected following imlifidase treatment but intact IgG BCR reappeared around Day 4 and the IgG pool starts to rebound by Day 7. Given that there is no permanent impairment to the total IgG pool or its ability to reconstitute, there were no reported long term infectious complications associated with imlifidase itself. The incidence and pattern (including infectious agent) of serious or severe infections were not different from those	new presentation of their clinical data, including the rate of infection. • Following the pre-meeting briefing for NICE appraisal committee 1, the ERG submitted to the company via the NICE team (05/03/2021) a list of clinical data points it considered would be useful in the appraisal of imlifidase, including infection rates in the target patient population, and in the subgroup of patients who received a 2nd dose. In its re-submission, the company did not provide these infection rate data. • At clarification to their re-submission, the ERG provided the company with a table to complete the clinical data it required for its appraisal of imlifidase, including infection rates in the target patient populations, and in the subgroup of patients who received a 2nd dose. As noted in the ERG response, the

		observed in kidney-transplanted patients in general and included mainly upper respiratory and urinary tract infections (n = 15).	company deleted this row when returning the table and the data were not presented. The ERG further note that the infection data referred to in the company's FAC response fails to include event rates specific to the target patient population for imlifidase. In its original appraisal, clinical advisors to the ERG raised the importance of understanding infection rates with a drug such as imlifidase because of the complete depletion of immunoglobulin. Hence, infections, particularly respiratory tract infections, are of potential concern with imlifidase treatment as these are the most common infections in patients with hypogammaglobulinemia. The ERG is uncertain whether infection rates would be expected to be higher in more sensitised patients than those in the broader trials of imlifidase, and so had requested these data for clarity. The ERG does not consider a text statement to claim that infection rates in the target patient subgroups were "not significantly different" (company re-submission) to be sufficient, given the lack of clarity as to whether the

			company conclusion is based on statistical significance, which would be impossible to achieve in a sample of this size.

Issue 7 Details on the PAES study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Hansa would like to add more detail to the PAES study design Pg 22; Section 3.5	UK approved study sites include [redacted]	To further reinforce the relevance of data being collected in the PAES study to inform NICE decision making	Not a factual inaccuracy. This information was not provided to the ERG, and it would appear the PAES study is not yet ongoing, and thus still subject to change.

Issue 8 Minimising of Cold Ischaemic Time (CIT)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG raises the potential extended CIT as a risk to outcomes for imlifidase-enabled transplantation • Pg 7; Section 3.2 • Pg 8; Section 3.2.1 • P8; Section 3.2.2 • Pg 10 Section 3.2.2	To remove the comment that Hansa accepted Figure 1 provided by the ERG To acknowledge the clinical expert opinion and recognise that while it is expected that CIT may be extended by a few hours for imlifidase-enabled	Hansa is working with clinicians to develop the imlifidase treatment protocol taking into account multiple clinical variables, including minimizing CIT. Clinician opinion obtained indicates that the anticipated increased CIT is not a major concern associated with the use of imlifidase. Hansa has spoken to 3 expert clinicians this	Not a factual inaccuracy. The Figure 1 presented by the ERG and commented on by the company during clarification shows the potential timescales involved in the treatment pathway for imlifidase. The figure shows multiple patient pathways, depending upon how many

	transplants, this will not reach the limit of what clinicians consider "reasonable" To include that Hansa is working with clinicians to develop the imlifidase treatment protocol taking into account multiple clinical variables, including minimizing CIT	week (Dr Rommel Ravanan, Dr Adnan Sharif and Prof. Nithya Krishnan, all speaking to us in a personal capacity), and specifically asked their thoughts about this topic. All 3 responded that they were not overly concerned about the increase in CIT in light of other considerations (not least the benefit of the patient receiving a transplant that he/she would not otherwise get). • In the US, it is not uncommon for CIT to reach 24 hours. In the UK, CIT is significantly lower. Targets are for <12 hours on average for a DCD transplant, <18 hours for a DBD. • Standard of care at 2 out of 3 centres which we spoke to is virtual cross match. We know this is the case for a 4th centre as well, whom we spoke to in early December. 2 of the lead clinicians out of the 3 we spoke to this week have said that they would be satisfied using the result of the virtual crossmatch to decide to go ahead with an imlifidase transplants (of those, 1 commented that if a second imlifidase infusion was required, a wet crossmatch would be needed). One of these clinicians commented that they expect the CIT for an imlifidase enabled transplant to be 18 to 24 hours, which they described as "reasonable". • One clinician said that although they would be comfortable with this themselves, and the lab would also be	crossmatch tests and how many doses of imlifidase patients receive, with a range in time for each step in the pathway shown to represent the estimates given by the company and by clinical experts to the ERG. Inherently, the worst case scenario would be where a patient requires both multiple tests and multiple doses of imlifidase, and where a maximum period of time is required for each of these stages. This is a plausible scenario based on the clinical trial data and the estimates provided by the company and clinical advisors, though as noted in its response, clinical advisors to the ERG considered that the longer times may only be experienced by a minority of patients in the NHS. The ERG also noted in its response that its clinical advisors proposed ways in which timelines may be reduced, and that the company plans to further refine the timeframe with NICE. Clinical advisors to the ERG noted that increasing CIT is associated with poorer transplant outcomes. Given the lack of long-term data about the survival of transplants following treatment with imlifidase, the ERG consider the potential CIT of patients treated with imlifidase to be a relevant factor for consideration by the

		happy with this, they suspect that surgeons would be reluctant in their centre. However, they do not feel that this will increase CIT significantly. This is because the wet crossmatch is likely to take place concomitantly with other existing and required activities such as contacting the patient and bringing them in, consenting the patient, "prepping" them, undertaking dialysis if required, etc. Transplant teams are used to progressing many activities in parallel in the run up to the surgery itself, this would be one more thing and will not add the full length of the crossmatch test result time to the cold ischaemia time. As an example, transplant patients need to take a Covid test, the result of which takes 1 hour to generate, and this has not increased CIT because it is done in parallel with other activities. In addition, one clinician commented that they get wet / cellular crossmatch results in 4 hours, not 6. One clinician commented that the alternative for these patients is to remain on dialysis. 5 to 10 years on dialysis instead of a transplant has significant quality of life and health consequences. This needs to be taken into account when considering the appropriateness of a longer (but still clinically acceptable) cold ischaemia time. Hansa agrees with the ERG as stated in Section 3.2.2 The ERG acknowledges that as a new technology, the treatment	committee.

		pathway for imlifidase may be refined with experience and considered it appropriate that it remains under review by the company and its clinical advisors. Hansa also aligns with clinical advice given to ERG as stated in 3.2.2 “Clinical advice to the ERG was that reducing CIT was important for ensuring that patients achieve the best possible outcome following treatment, but that some small risk of wastage of the kidney may be acceptable to clinicians, as a small risk of wastage is a currently accepted risk within the KOS.” The care pathway provided by the ERG (Figure 1 in your letter dated 16 November) outlines what the maximum CIT is in the worst-case scenario (2 infusions and no crossmatch results in less than 6 hours), and clinical experts have told us that this is not representative of their expectation in clinical practice. In the 3 years data[2] the mean total CIT for patients who were considered cross-match positive was 21.0 hours (n=39) and had allograft survival at 3 years of 84%.	

Issue 9 The number of DSA Testing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG queried the number of	“the company states that up to 4	Clinical expert opinion sought from multiple	Not a factual inaccuracy.

additional DSA tests required for an imlifidase transplantation • Pg 8, 10, 30	crossmatch tests may be needed for a single patient, *based on feedback from multiple UK clinical experts in this setting,* although evidence presented at clarification showed an average of 4.2 crossmatch tests per patient in the newly defined patient population, implying that some patients may need more than 4 tests	UK experts on the imlifidase treatment pathway suggested that a maximum of 4 cross-match tests would be sufficient. Therefore, the need for more than 4 tests in the UK would be extremely rare. However, Hansa will align with the ERG assumption based on the evidence. To reflect current alignment of economic model assumptions, Hansa is amending the simple PAS to [redacted] discount	The heading of Issue 9 and the "Description of problem" refer to DSA testing however, the "Description of proposed amendment" and "Justification for amendment" refer to crossmatch testing. The ERG acknowledges the uncertainty, and thus took data from the clinical studies provided by Hansa.

Issue 10 Proportion of Patients needing a 2nd dose

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>The ERG have queried the proportion of patients who required a second dose in the "all imlifidase" population cohort within the trial data: 6.5% vs 8.7%

Pg 36, 44, 46, 48</td>
<td>Removal of 8.7% from base case</td>
<td>Hansa would like to sincerely apologise for the error in the table provided. Table 1 in the ERG report and Table 2 in Hansa response (dated 22 Nov 21) should be as follows
<table>
<tr><th></th><th>Newly defined patient population</th><th>'Unlikely to be transplanted'</th><th>'All imlifidase' population</th></tr>
<tr><td>Number of patients who received 2 doses of imlifidase</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Therefore we recommend that the ERG base case ICER be</td>
<td>The ERG thanks the company for correcting this error in their submission.

Given the timescale available to the ERG, it was not possible for the ERG to revise all of its analyses with the correction. However, the ERG has updated the ERG base case to reflect the change.</td>
</tr>
</table>

		amended accordingly please.	

Issue 11 Re-transplantation inclusion in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG queried whether patients being re-transplanted should be included in the model Pg 38	Hansa chose to not include re-transplantation which is a conservative assumption.	Hansa accepts the ERG assumption however it can be argued here that not including re-transplantation is a conservative assumption. In the Hansa model, only the comparator arm patients have access to a compatible transplant within the first four cycles of the model. If a compatible re-transplant was possible for example in the two years following a graft loss, the imlifidase treatment arm would benefit more from a re-transplant than the comparator arm as there are more patients that are transplanted in the imlifidase group, so more graft loss and therefore a greater potential of re-transplant. To reflect current alignment of economic model assumptions, Hansa is amending the simple PAS to [redacted] discount	Not a factual inaccuracy. The ERG recognise this is a limitation of the model, and the available evidence. We note the potential for further transplants on both arms, though would not consider it conservative, as it would increase costs (and potentially QALYs) on the arm with more transplant. The balance between these (and the effect on kidney availability in others) would then determine whether this renders imlifidase more or less cost effective. For this reason it remains an unknown.

Issue 12 SoC patients to begin in the transplant health state at cycle 0

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG wanted to include SoC to begin in the transplant health state at cycle 0 Pg 44	Recommend removal of assumption	Hansa disagrees with this assumption as the decision problem of the model is that at model entry, the patient has a positive crossmatch with a potential donor. Therefore, at Day 0 of the model, the patient can either receive imlifidase and have access to this kidney or does not use imlifidase and needs to remain on dialysis until there is a compatible donor. If there is a compatible donor at cycle 0, there is no reason to use imlifidase.	Not a factual inaccuracy. The ERG disagrees with changing the assumption; the model includes cycles which are 6 months long, with a constant probability of a donor kidney becoming available – this is as likely on day 1 as day 101. For this reason, the ERG believes the current input to be correct.

Issue 13 ERG Assumption for Graft Survival in the cost effectiveness model [redacted]

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG used the iBox predictive model to inform graft survival and applied a 0.9	Recommend amendment of ERG base case assumption for graft survival	Hansa disagree with the ERG's recommendation to use the iBox extrapolation with a 0.9 HR as the base case for the graft survival assumption within the Markov model. Hansa still recommend the base case using the imlifidase 3-year data graft survival extrapolation for NICE decision making. Our reasons for this are as follows: 1. Hansa approached 3 clinical experts in the UK on this question, this past week (this includes Dr Sharif). All 3 have stated that they do not understand the logic of applying a hazard ratio to the iBox curve, and they agree that basing the graft survival extrapolation on imlifidase-treated patients included in the published 3-year data is a reasonable option. 2. We received feedback from Professor Nithya Krishnan at University Hospitals	Not a factual inaccuracy. The ERG believe their base case to be reasonable, and do not propose to change it. The ERG note that the company's response was received by the ERG approximately 20 minutes before

hazard ratio (HR). Pg 31		Coventry and Warwickshire (UCHW) who has published a paper in 2021 investigating long-term graft and patient survival for highly sensitized and difficult to match patients. The UCHW is a leading UK centre in the area of highly sensitised transplantation and representative of a centre that would be performing imlifidase enabled transplantations in the future. The study has higher relevance to this appraisal compared to the Manook et al[3] study quoted by the ERG as: • The Krishnan et al[4] study assessed graft survival for an HLA incompatible (HLAi) population where 12% of the cohort had a deceased donor transplantation, which included highly sensitised patients (who were pregnant or had previous transplants), unlike the HLAi analysis conducted in the Manook study which had no DD patients. • The Krishnan[4] study is over a broader period and contains more recent data (2018) compared to Manook study (2013), and between these timeframes, there have been significant advancements in terms of the management of transplant rejection. 3. Professor Krishnan recommended that the HLAi analysis in their study was a robust surrogate for graft survival outcomes for imlifidase patients. Further, the 5- and 10-year graft survival probabilities of the 3-year data extrapolation compared to the HLAi analyses are more conservative. This is also the case when compared with NHSBT data collected up to 2015 for deceased donors.[5] Please see table below: **Source** / **Five year Graft Survival** / **Ten year Graft Survival** NHSBT 2007-2009, DCD[5] / 0.86 / 0.75 NHSBT 2013-2015, DCD[5] / 0.86 / - NHSBT 2007-2009, DBD[5] / 0.85 / 0.74	the call mentioned in the company's response, which is why the issue was not raised at that time. The ERG report details the reasons for preferring extrapolation based on iBox, which essentially relate to non-proportional hazards, the low number of events in the company data, the short follow up in the company data, and thus the limited ability to extrapolate. As the committee felt the graft survival projections in the original company base case (iBox estimates) were too optimistic, the ERG felt the Company's use of the clinical trial data to inform graft survival did not address these concerns as the 5 and 10 year estimates were even more optimistic than that of the iBox. The use of a hazard ratio applied to iBox reflects the input seen by the ERG (including in the committee meeting) which includes the increase in CIT, the incompatibility of donors, and patients starting in a worse health state (with more prior transplants).

		NHSBT 2013-2015, DBD[5] 0.87 - Krishnan et al, 2021[4], HLAi cohort 0.85 0.70 Imlifidase iBox 0.76 0.61 Imlifidase iBox, HR = 90% 0.74 0.58 All imlifidase extrapolations 0.82 0.68 UTT imlifidase extrapolations 0.83 0.68 DBD = Donors after Brain Death DCD = Donors after Cardiac Death UTT = unlikely to be transplanted 4. We understand that the ERG's recommendation to use the iBox extrapolation with a 0.9 HR stems from the opinion of 1 expert. Out of 3 experts consulted by the ERG, one provided this view and two stated that they could not provide a recommended approach to estimate long-term graft survival for imlifidase. Hansa could not review the ERG rationale for the quantification of this assumption as no insight into the one clinician feedback could be provided. Hansa spoke to Dr Sharif, a consultant Nephrologist at the Queen Elizabeth Hospital Birmingham, who also could not see the justification behind the rationale for the 0.9 HR ERG assumption and recommended that the iBox tool, without additional hazard ratios added, may be a pertinent supplementary tool for appraisal estimation of graft survival. However, the primary trial evidence would be the most appropriate evidence source. In conclusion, Hansa disagree with the recommendation by the ERG to use the iBox curve with a 0.9 HR added. We have provided our multiple reasons above. We maintain that the imlifidase clinical trial evidence is the most appropriate data source in the absence of imlifidase clinical experience in the UK. As such, this data should form the basis of estimating graft survival post imlifidase-enabled kidney transplantation. Additionally, Hansa recommends the ERG to consider using the Krishnan paper[4] as their	In the absence of robust long-term data, the application of a HR to the iBox estimates enables the committee to observe the results of the cost-effectiveness analysis when the estimates of graft survival are less optimistic. The intention of applying a HR to iBox was the ERG's solution to try and address the committee's comments from the first ACM.

		external source of validation for the graft survival data. This is a critical issue that we would like to resolve before the second appraisal committee on the 10th of February. Hansa are open to a call with the ERG to this end. We note that this point was not raised when we did have a call to discuss our revised base case, on 23 November 2021.	

Issue 14 PSA results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states that both the base case and mean PSA results were the same as those presented in the original company base case Pg 41	Recommend removal	The PSA were re-run in the version submitted and the results were not the same as in the original version submitted	The ERG report is correct. The ERG report refers to the base case and PSA results in Table 6 of the Company's response to ERG questions being incorrect. Table 6 of the Company's response to ERG questions (dated 22/11/2021 in the file name) was labelled "Reference case probabilistic results: [redacted]" and presents results identical to the original company base case shown respectively below (taken from version 2.1 of the Company model, dated 16/11/2020):

			 Though the PSA results in the Company's updated model were different to those in the company's Table 6, it was unclear to the ERG whether the PSA in the model had been run with all settings set to the updated company base case. As a result, the ERG chose to rerun the PSA to ensure the correct presentation of all results.

Issue 15 Error in ERG Model: Transplanted Cycle

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Hansa have identified an error in the ERG model	Correction of the cells O6 to O120 so they are linked to the appropriate probability of graft loss.	There is an error in the Markov tunnel state "Transplanted Cycle 4" formula when the assumption "patients in SOC arm receive a transplant at cycle 0" is selected: Starting at Cycle 6 and beyond, the graft survivals are linked to the wrong graft loss probability. For example, Cycle 6, which is the third post-transplant cycle for these patients, is linked to the first-cycle probability of graft loss. Cycle 7 (4th post-transplant cycle) is linked to the third post-transplant probability, etc.	Error corrected in ERG model. This resulted in an increase in the ICER from £40,952 to £40,995 (prior to correction of imlifidase 2nd dose percentage).

Location of incorrect marking	Description of incorrect marking	Amended marking
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	[redacted]
ICERs can be unredacted for decision making purposes	ICERs listed on pages 39, 41, 42, 48, 49, 50	[redacted]hank you for highlighting this – we have removed the redaction.

References

[1] Jordan et al. Imlifidase Desensitization in Crossmatch-positive, Highly Sensitized Kidney Transplant Recipients: Results of an International Phase 2 Trial (Highdes Transplantation 2021;105: 1808–1817
[2] Kjellman C, Maldonado AQ, Sjöholm K, Lonze BE, Montgomery RA, Runström A, et al. Outcomes at 3 years post-transplant in imlifidase-desensitized kidney transplant patients. Am J Transplant. 2021.
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[4] Krishnan et al. HLA Antibody Incompatible Renal Transplantation: Long-term Outcomes Similar to Deceased Donor Transplantation. Transplant Direct. 2021 Aug; 7(8): e732.
[5] NHSBT Organ and Tissue Donation and Transplantation Activity Report 2020/21 activity-report-2020-2021.pdf (windows.net)

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]

A Single Technology Appraisal

ERG response to queries raised by NICE ahead of appraisal committee meeting 2

Produced by

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Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This response is linked to ERG report	Farmer C, Knowles E, Kiff F, Long L, Robinson S, Nikram E, Powell R, Moore J, Griffin S, Hatswell A, Crathorne L, Melendez-Torres G.J. Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]. Peninsula Technology Assessment Group (PenTAG), 2020.

1. ERG BASE CASE RESULTS - [redacted]

The ERG have removed the preferred assumption of [redacted] of patients receiving a second dose of imlifidase from the ERG base case following a correction by the company to Table 2 (company's response to ERG questions), sent to the ERG in the second FAC of the imlifidase appraisal (FAC 2, issue 10). In addition, an error was corrected in the application of the ERG's preferred assumption allowing the SoC patients to begin the model in the transplant health state (FAC 2, issue 15).

Table 1 (corresponding to Table 12 of the ERG response to company updated submission) presents the ERG's preferred model assumptions including a [redacted] following this clarification.

Table 1: ERG's preferred model assumptions – [redacted]

Preferred assumption	Section in ERG response to company's revised submission	Individual change to corrected ICER £/QALY	Cumulative ICER £/QALY
Company base case	*Section 5.1*	-	29,589
Allow 5% of SoC to receive 'no dialysis'	*Section 4.1.3 & 6.1*	30,323	30,323
Increase number of crossmatch tests to 2.4	*Section 4.1.6 & 6.1*	29,722	30,457
Use iBox predictions to inform graft survival with a 0.9 HR	*Section 4.1.9 & 6.1*	38,189	39,152
Allow SoC patients to begin the model in the transplant health state	*Section 6.1*	31,005	39,639

Abbreviations: ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; SoC, standard of care.

A comparison of the revised company's base case analysis and the revised ERG's preferred analysis results are presented in Table 2 (corresponding to Table 12 of the ERG response to company updated submission). The equivalent results of PSA using the ERG preferred assumptions are also provided.

Table 2: Comparison of company and ERG results - [redacted]

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,589
ERG base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,639
ERG corrected company probabilistic base case*							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,837
ERG base case (probabilistic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,146

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year

Notes: It was not possible to obtain PSA LY results from the cost-effectiveness model.

* ERG re-run of the PSA using the company's base case assumptions

A comparison of the company's and ERG's scenario analyses using the ERG's revised preferred assumptions versus the company's base case, including a [redacted], is provided in Table 3 (corresponding to Table 14 of the ERG response to company updated submission).

Table 3: Comparison of company and ERG scenario analysis results - [redacted]

Scenario	ICER (£/QALY)	
	Company	ERG
Base case	£29,589	£39,639
Company scenario analyses		
Time horizon – 10 years	£78,174	£98,488
Time horizon – 20 years	£36,904	£49,486
Graft loss extrapolation – iBox*	£34,855	£36,241
Graft loss extrapolation – All imlifidase patients	£29,935	£31,232
OS with a functioning graft – 'Unlikely to be transplanted' patients	£48,191	£66,425
No caregiver disutility	£30,549	£40,945
Caregiver disutility source – Nagawasa *et al* (2018)[6]	£30,147	£40,399
ERG scenario analyses		
Utility source – Cooper *et al* (2020)[5]	£30,011	£40,116
Proportion of imlifidase patients to receive a transplant – 94.4%	£30,903	£41,171
Proportion of imlifidase patients to receive a transplant – 90%	£34,318	£45,156
Proportion of imlifidase patients to receive a transplant – 99%	£27,773	£37,523

Scenario	ICER (£/QALY)	
	Company	ERG
SoC annual compatible transplant rate – 5%	£26,229	£35,523
SoC annual compatible transplant rate – 10%	£31,977	£42,576
SoC annual compatible transplant rate – 15%	£38,713	£50,917
SoC proportion on 'no dialysis' – 0%	£29,589	£38,854
SoC proportion on 'no dialysis' – 10%	£31,058	£40,423
Number of crossmatch tests following a full dose of imlifidase - 1	£29,589	£39,485
Number of crossmatch tests following a full dose of imlifidase – [redacted]	£29,881	£39,821
Number of DSA tests - 1	£29,312	£39,356
Number of DSA tests - 6	£30,003	£40,063
Apply HR to iBox graft estimates – 0.80	£42,486	£44,017
Apply HR to iBox graft estimates – 0.85	£40,193	£41,681
Apply HR to iBox graft estimates – 0.95	£36,422	£37,839
Proportion of imlifidase patients to receive a second dose – [redacted]%	£30,074	£40,199
Proportion of imlifidase patients to receive a second dose – [redacted]%	£30,391	£40,566
Proportion of imlifidase patients to receive a second dose – [redacted]%	£33,752	£44,449
Apply alternative transplant cost - £21,000	£30,898	£41,153
Change OS dialysis source – ERA-EDTA	£31,302	£40,015
Apply HR to "Unlikely to be transplanted" graft survival – 0.9 **	£32,085	£33,426
Apply HR to "Unlikely to be transplanted" graft survival – 0.98 **	£30,044	£31,344

Abbreviations: ERA-EDTA, European Renal Association – European Dialysis Transplant Association; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life-year.

Note: * iBox data to inform graft survival is applied with no HR in this scenario.

** "Unlikely to be transplanted" data is used to inform graft survival in these scenarios.

2. ERG AND COMPANY BASE CASE RESULTS - [redacted]

The company have proposed a change to their PAS to a [redacted] Table 4 (corresponding to Table 13 of the ERG response to company updated submission) presents the company's and ERG's deterministic and PSA base case results (including corrections to the proportion of imlifidase patients to receive a second transplant and calculation error in the ERG preferred assumption 4), including a [redacted].

Some of the ERG's assumptions appear to have been accepted by the company at the second FAC (Issue 2: allowing a proportion of comparator patients to receive dialysis and Issue 9: increasing the number of crossmatch tests); however. it was not clear what the company preferred as their new base case. Therefore, the ERG have not made these amendments so as not to introduce further confusion. The only change to the company's base case in Table 4 is the change to the PAS discount. It is expected the true value of the company's base case and probabilistic ICERs to be greater than those reported in Table 4, should some of the ERG assumptions have been implemented into the company's base case.

Table 4: Comparison of company and ERG results - [redacted]

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,754
ERG base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,525
Company base case (probabilistic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,210
ERG base case (probabilistic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,971

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year

Notes: It was not possible to obtain PSA LY results from the cost-effectiveness model.

* ERG re-run of the PSA using the company's base case assumptions

A comparison of the company's and ERG's scenario analyses using the ERG's preferred assumptions versus the company's base case, including a [redacted] is provided in Table 5 (corresponding to Table 14 of the ERG response to company updated submission).

As with Table 4, the only change to the company's base case in Table 4 is the change to the PAS discount and does not include the acceptance of the ERG assumptions mentioned in the company's FAC 2. It is expected the true value of the company's ICERs to be greater than those reported in Table 5, should some of the ERG assumptions have been implemented into the company's base case.

Table 5: Comparison of company and ERG scenario analysis results - [redacted]

Scenario	ICER (£/QALY)	
	Company	ERG
Base case	£27,754	£37,525
Company scenario analyses		
Time horizon – 10 years	£73,295	£93,117
Time horizon – 20 years	£34,419	£46,679
Graft loss extrapolation – iBox*	£32,863	£34,236
Graft loss extrapolation – All imlifidase patients	£28,089	£29,374
OS with a functioning graft – 'Unlikely to be transplanted' patients	£44,613	£62,323
No caregiver disutility	£28,655	£38,762
Caregiver disutility source – Nagawasa *et al* (2018)[6]	£28,278	£38,244
ERG scenario analyses		
Utility source – Cooper *et al* (2020)[5]	£28,151	£37,977
Proportion of imlifidase patients to receive a transplant – 94.4%	£29,026	£39,008
Proportion of imlifidase patients to receive a transplant – 90%	£32,332	£42,866
Proportion of imlifidase patients to receive a transplant – 99%	£25,997	£35,477
SoC annual compatible transplant rate – 5%	£24,503	£33,540
SoC annual compatible transplant rate – 10%	£30,066	£40,370
SoC annual compatible transplant rate – 15%	£36,585	£48,446
SoC proportion on 'no dialysis' – 0%	£27,754	£36,741
SoC proportion on 'no dialysis' – 10%	£29,224	£38,310
Number of crossmatch tests following a full dose of imlifidase - 1	£27,754	£37,371
Number of crossmatch tests following a full dose of imlifidase – [redacted]	£28,046	£37,708
Number of DSA tests - 1	£27,478	£37,243
Number of DSA tests - 6	£28,169	£37,949
Apply HR to iBox graft estimates – 0.80	£40,247	£41,764

Scenario	ICER (£/QALY)	
	Company	ERG
Apply HR to iBox graft estimates – 0.85	£38,029	£39,503
Apply HR to iBox graft estimates – 0.95	£34,380	£35,783
Proportion of imlifidase patients to receive a second dose – [redacted]%	£28,224	£38,068
Proportion of imlifidase patients to receive a second dose – [redacted]%	£28,531	£38,422
Proportion of imlifidase patients to receive a second dose – [redacted]%	£31,784	£42,181
Apply alternative transplant cost - £21,000	£29,064	£39,039
Change OS dialysis source – ERA-EDTA	£29,747	£38,236
Apply HR to “Unlikely to be transplanted” graft survival – 0.9 **	£30,167	£31,496
Apply HR to “Unlikely to be transplanted” graft survival – 0.98 **	£28,194	£29,482

Abbreviations: ERA-EDTA, European Renal Association – European Dialysis Transplant Association; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life-year.

Note: * iBox data to inform graft survival is applied with no HR in this scenario.

** “Unlikely to be transplanted” data is used to inform graft survival in these scenarios.

3. GRAFT SURVIVAL OPTIONS

Table 6 presents the graft survival predictions for the three options in the company's model (iBox, Unlikely to be transplanted and All imlifidase) and an additional two analyses by the ERG where a HR is applied; 0.9 (as per the ERG base case) and 0.8 (as per NICE request).

Table 6: Graft survival predictions

	5-year survival	10-year survival	20-year survival
iBox predictions, with Weibull extrapolation (Original company & ERG base case)	[redacted]	[redacted]	[redacted]
Unlikely to be transplanted, with exponential extrapolation (revised company base case)	[redacted]	[redacted]	[redacted]
All imlifidase, with exponential extrapolation	[redacted]	[redacted]	[redacted]
iBox predictions, with Weibull extrapolation and 0.9 HR (ERG revised base case)	[redacted]	[redacted]	[redacted]
iBox predictions, with Weibull extrapolation and 0.8 HR (NICE requested scenario)	[redacted]	[redacted]	[redacted]

Statement by Patient Representative

I apologies for not being able to join you at the meeting.

In my absence I would like in a few words to try to encourage and help you to better understand some of the challenges a renal patient faces, to empathise with their predicament. “To walk a mile in someone else's shoes”

You may have “crash landed” as a renal patient, suddenly having renal failure or it may have been a long progressive decline in renal function.

You are reliant and tied to dialysis with all the challenges that entails, diet, fluid restrictions, interruptions to social life, relationships more difficult, work commitments difficult to fulfil etc.

You have realised chronic renal disease is a life long illness and imposition!

You could be any age with a variety of life opportunities or challenges ahead.

You might be in your teens and your schooling has been interrupted by your illness, but you want to go to university. Or your friendships are threatened because of time in hospital and for treatments.

You might be in your twenties or thirties with a new partner and young children to support. Maintaining your economic independence is vital to you and your loved ones. Just having the energy to play with the kids is problematic.

You may be in your fifties and have elderly parents who need to be cared for but you don’t have the energy or are too ill yourself to support them as you want.

Or it might be later in life and you want to enjoy your retirement and care for your partner. All those years working hard, looking forward retirement, to world travel, or taking up a hobby. Now all threatened and taken away.

In summary, chronic renal disease can seriously impact on all aspects of your life, relationships, financial, career, social, learning, mentally, physically and many more.

As well as the impact on daily life you have become aware that dialysis, although it maintains your life has many serious long term implications such as heart disease, bone disease, nerve disease, risk of infections to name a few. You have also realised long term dialysis shortens life expectancy. All these fears and realisations are with you every day. You are scared and worried.

Statement by Patient Representative

Your renal physician suggests a transplant which will give you freedom to live a normal life without restrictions, it gives you back control, the health to fulfil your full potential and grasp all of life's opportunities, and the energy and time to fulfil your desires. It is the light at the end of the long tunnel of dialysis and renal failure. You have "hope"!

Then you have various pre transplant tests and are told you can't have a transplant because it will be rejected. All hope is stolen from you! The rug is pulled from under you again!

An analogy might help you understand how this might feel. As someone who is clinically extremely vulnerable I should say I totally support all the covid safeguards we have endured, but we have all seen and experienced the wiriness and frustrations with the covid restrictions which have only been with us for around two years. How would you feel if we were now all told that a new covid variant has developed and we are back to March 2020 and have to go through the last two years again, and because there is a limited prospect of new drugs the restrictions will be for the rest of your life!

This is why finding new treatments that allow kidney patients who would reject their organ transplant is so vitally important. I hope this short statement helps you understand why imlifidase could be so crucial and meaningful in the life of a kidney patient.

Richard
Richard Ayres - Patient Representative

Bio
I have been a renal patient since 1977. I was on dialysis for two and a half years. I have had two kidney transplants, the first lasted three months and my current transplant was performed in 1980, 42 years ago.

Successful transplantation has allowed me to work full time at a senior level for 35 years, pay my taxes, travel extensively to nearly 40 countries, crew in a year long yacht race around the world, obtain a masters degree while working full time, sail single handed round the UK and and care for elderly relatives.