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

Authors

Caroline Farmer[1]
Emma Knowles[1,2]
Fraizer Kiff[1]
Linda Long[1]
Sophie Robinson[1]
Elham Nikram[1]
Richard Powell[3]
Jason Moore[3]
Siân Griffin[4]
Louise Crathorne[1]
Anthony. J. Hatswell[1,2]
G.J. Melendez-Torres[1]

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
2 Delta Hat, Ltd. Nottingham, UK
3 Royal Devon and Exeter NHS Foundation Trust, Exeter
4 University Hospital of Wales, Cardiff

Correspondence to

Caroline Farmer
3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; c.farmer@exeter.ac.uk

Date completed 12/11/2020

Source of funding This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/18/18.

Declared competing interests of the authors	None
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).
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 report should be referenced as follows	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]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2020.

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.

Table of Contents

List of key issues

List of tables

List of Figures

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.

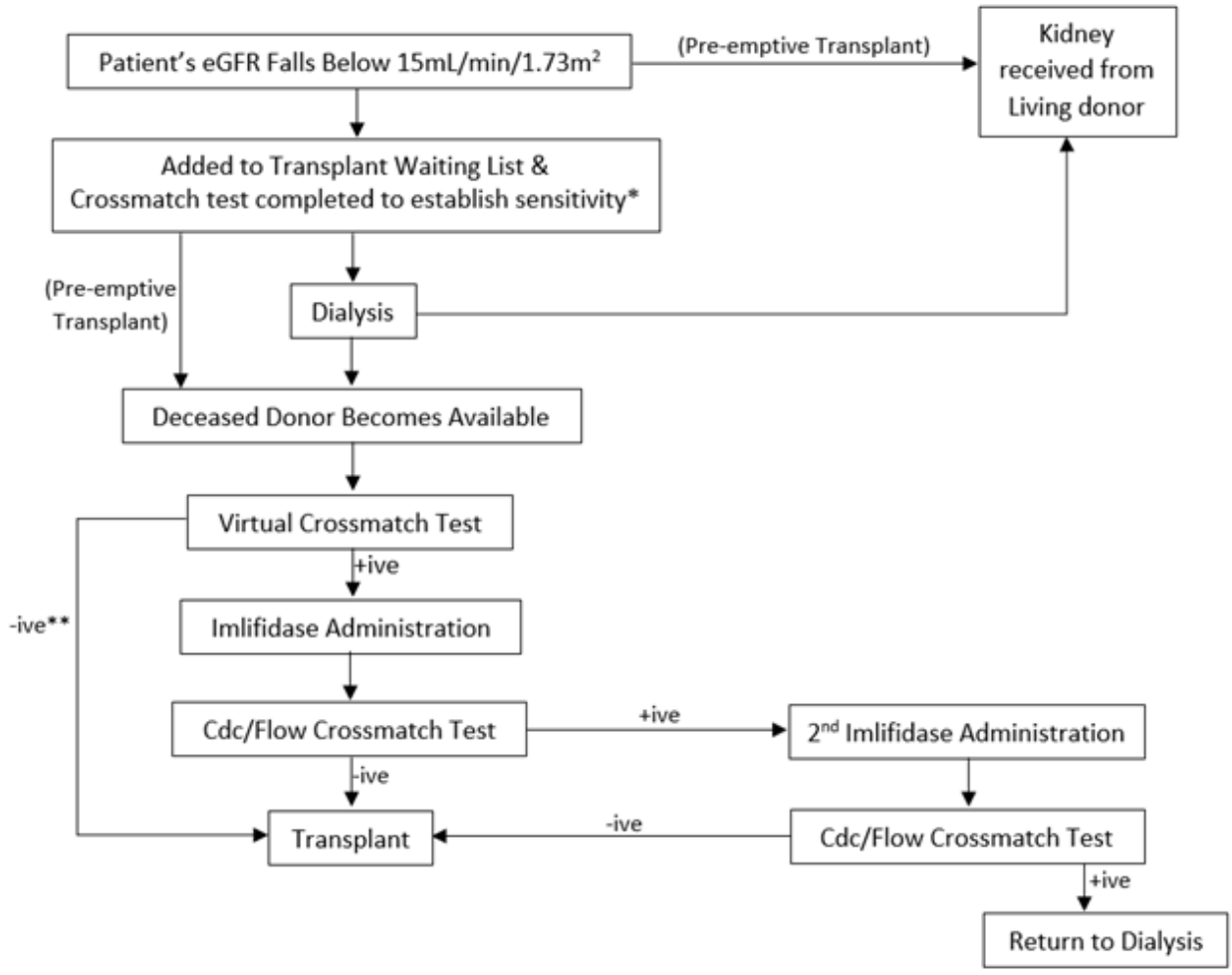
Based on the information provided in the CS, there also remains uncertainty around the timings of organ retrieval and the administration of imlifidase in the treatment pathway. Noting that a crossmatch test is need to determine whether imlifidase has been successful before a transplant can occur, the 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 7). 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

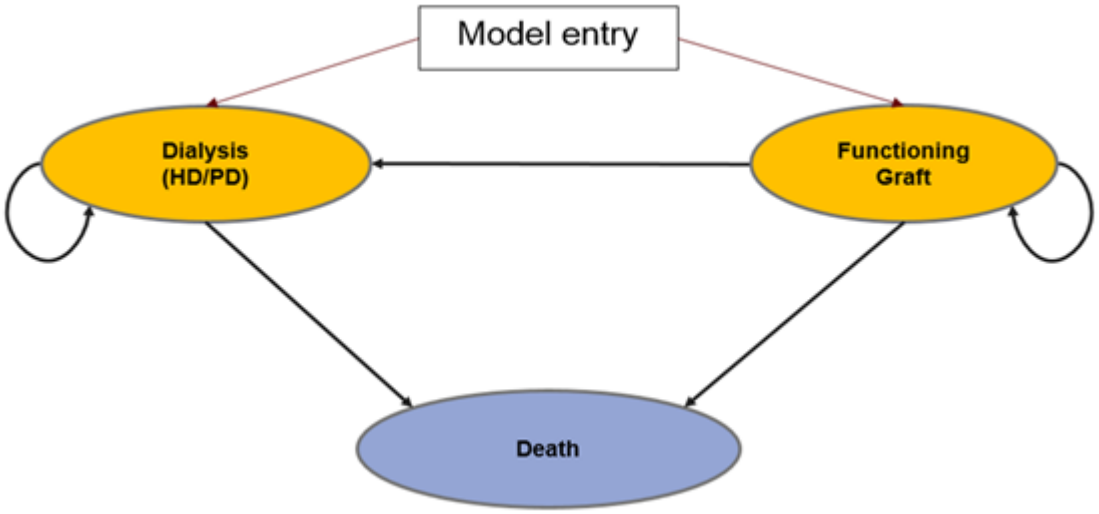
Systematic review step	Reference case	ERG comment on company's submission
	outcomes between the technologies being compared	the up front costs and downstream benefits of the technology
Synthesis of evidence on health effects	Based on systematic review	Although not based on systematic review, the evidence 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.

References

1. NHS. Chronic kidney disease. 2019.
2. National CKD Audit. National Chronic Kidney Disease Audit (Part 2). https://www.hqip.org.uk/resource/national-chronic-kidney-disease-audit-national-report-part-2/#.X5rxSlj7Spo (last accessed
3. Public Health England. *Chronic Kidney Disease Prevalence Model*. 2014. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/612303/ChronickidneydiseaseCKDprevalencemodelbriefing.pdf
4. NHS Blood and Transplant. 2019/20 Annual Report and Accounts.
5. Aufhauser Jr DD, Peng AW, Murken DR *et al.* Impact of Prolonged Dialysis Prior to Renal Transplantation. *Clin Transplant* 2018; **32:** e13260.
6. N.H.S. Blood Transplant. *Annual report on kidney transplantation report for 2018/2019 (1 April 2009 – 31 March 2019)*. 2019. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16778/nhsbt-kidney-transplantation-annual-report-2018-19.pdf
7. NHS Blood and Transplant. *Kidney Transplantation: Deceased Donor Organ Allocation*. 2019. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16915/kidney-allocation-policy-pol186.pdf
8. Manook M, Koeser L, Ahmed Z *et al.* Post-listing survival for highly sensitised patients on the UK kidney transplant waiting list: a matched cohort analysis. *Lancet* 2017; **389:** 727-734.
9. NHS Blood and Transplant. Personal communication, 2020.
10. Kidney Care UK. Facts and Stats. https://www.kidneycareuk.org/news-and-campaigns/facts-and-stats/ (last accessed
11. Jordan SC, Lorant T, Choi J *et al.* IgG endopeptidase in highly sensitized patients undergoing transplantation. *N Engl J Med* 2017; **377:** 442-453.
12. EMA. *Assessment report - Iderifix*. 2020. https://www.ema.europa.eu/en/documents/assessment-report/idefirix-epar-public-assessment-report_en.pdf
13. Parsons RF, Locke JE, Redfield RR, 3rd *et al.* Kidney transplantation of highly sensitized recipients under the new kidney allocation system: A reflection from five different transplant centers across the United States. *Human immunology* 2017; **78:** 30-36.
14. British Transplantation S. *Guidelines for the detection and characterisation of clinically relevant antibodies in allotransplantation*. 2015. https://bts.org.uk/wp-content/uploads/2016/09/06_BTS_BSHI_Antibodies-1.pdf

15. Winstedt L. Imlifidase for desensitization in sensitized kidney transplant patients: pooled analysis of phase 2 trials [abstract] *Transplant International* 2019; **32:** 62.
16. Hansa Biopharma AB. Personal communication, 2020.
17. Winstedt L, Järnum S, Nordahl EA *et al.* Complete removal of extracellular IgG antibodies in a randomized dose-escalation phase I study with the bacterial enzyme IdeS: a novel therapeutic opportunity. *PLoS One* 2015; **10:** e0132011.
18. Lorant T, Bengtsson M, Eich T *et al.* Safety, immunogenicity, pharmacokinetics, and efficacy of degradation of anti-HLA antibodies by IdeS (imlifidase) in chronic kidney disease patients. *Am J Transplant* 2018; **18:** 2752-2762.
19. Lorant T, Backman L, Tufveson G *et al.* Rapid removal of anti-HLA antibodies in immunized patients: Two dose finding studies of the IgG degrading enzyme IdeS. *Transplantation* 2016; **100:** S416.
20. Lorant T, Biglarnia A, Backman L *et al.* Rapid removal of anti-HLA antibodies in immunized patients awaiting renal transplantation-a dose finding study of the IGG degrading enzyme ides. *Transpl Int* 2015; **28:** 73.
21. Huang E, Choi J, Vo A *et al.* Three-year outcomes of highly-sensitized kidney transplant recipients desensitized with imlifidase (IdeS). *Am J Transplant* 2019; **19:** 588.
22. Jordan S, Choi J, Huang E *et al.* Follow up of patients treated with the IgG endopeptidase (IdeS) for desensitization and HLA incompatible (HLAi) kidney transplantation. *Am J Transplant* 2018; **18:** 447.
23. Jordan S, Choi J, Louie S *et al.* Experience with the bacterial enzyme ides (IgG Endopeptidase) for desensitization of highly-HLA sensitized (HS) kidney allograft recipients. *Am J Transplant* 2017; **17:** 266.
24. Jordan S, Choi J, Zhang X *et al.* Initial experience with the bacterial enzyme IdeS (IgG endopeptidase) for desensitization of highly-HLA sensitized (HS) patients. *Am J Transplant* 2016; **16:** 796-797.
25. Lonze BE, Tatapudi VS, Weldon EP *et al.* IdeS (Imlifidase): A novel agent that cleaves human IgG and permits successful kidney transplantation across high-strength donor-specific antibody. *Ann Surg* 2018; **268:** 488-496.
26. Keith DS, Vranic GM. Approach to the Highly Sensitized Kidney Transplant Candidate. *Clin J Am Soc Nephrol* 2016; **11:** 684-693.
27. Hatswell AJ, Baio G, Berlin JA *et al.* Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999–2014. *BMJ Open* 2016; **6:** e011666.

28. UK Renal Registry. *22nd Annual report; Data to 31/12/2018*. https://renal.org/sites/renal.org/files/publication/file-attachments/22nd_UKRR_ANNUAL_REPORT_FULL.pdf
29. Bartel G, Wahrmann M, Regele H *et al.* Peritransplant Immunoadsorption for Positive Crossmatch Deceased Donor Kidney Transplantation. *Am J Transplant* 2010; **10:** 2033-2042.
30. Schwaiger E, Eskandary F, Kozakowski N *et al.* Deceased donor kidney transplantation across donor-specific antibody barriers: Predictors of antibody-mediated rejection. *Nephrol Dial Transplant* 2016; **31:** 1342-1351.
31. Amrouche L, Aubert O, Suberbielle C *et al.* Long-term Outcomes of Kidney Transplantation in Patients With High Levels of Preformed DSA:The Necker High-Risk Transplant Program. *Transplantation* 2017; **101:** 2440-2448.
32. Pankhurst L, Hudson A, Mumford L *et al.* 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:** e181.
33. Redfield R, Zens T, Scalea J *et al.* Etiology, Incidence and Outcomes of the Highly Sensitized Kidney Transplant Patient [abstract]. *Am J Transplant* 2015; **15**: S3.
34. Redfield RR, Scalea JR, Zens TJ *et al.* The mode of sensitization and its influence on allograft outcomes in highly sensitized kidney transplant recipients. *Nephrology Dialysis Transplantation* 2016; **31:** 1746-1753.
35. Gayo LO, M. Alvarez, L. Gonzalez, E. Selgas, R. Jiminez, C. . P.035 Acute Rejection and Short-Term Outcomes in Highly Sensitized Kidney Transplant Recipients [abstract]. *Transplantation* 2018; **102**.
36. Heidt S, Claas FHJ. Transplantation in highly sensitized patients: challenges and recommendations. *Expert Rev Clin Immunol* 2018; **14:** 673-679.
37. Puttarajappa C, Shapiro R, Tan HP. Antibody-mediated rejection in kidney transplantation: a review. *Journal of transplantation* 2012; **2012:** 193724-193724.
38. Canadian Agency for Drugs and Technologies in Health. Database search filters. https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters (last accessed
39. Scottish Intercollegiate Guidelines Network. Search filters. https://www.sign.ac.uk/what-we-do/methodology/search-filters/ (last accessed
40. Jordan SC, Choi J, Vo A. Kidney transplantation in highly sensitized patients. *British Medical Bulletin* 2015; **114:** 113-125.

41. Loupy A, Aubert O, Orandi BJ *et al.* Prediction system for risk of allograft loss in patients receiving kidney transplants: International derivation and validation study. *BMJ* 2019; **366:** l4923.
42. 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.
43. Li B, Cairns JA, Draper H *et al.* Estimating health-state utility values in kidney transplant recipients and waiting-list patients using the EQ-5D-5L. *Value Health* 2017; **20:** 976-984.
44. Cooper JT, Lloyd A, Sanchez JJG *et al.* Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. *Health and Quality of Life Outcomes* 2020; **18:** 310.
45. Thomas GPA, Saunders CL, Roland MO *et al.* Informal carers' health-related quality of life and patient experience in primary care: evidence from 195,364 carers in England responding to a national survey. *BMC Family Practice* 2015; **16:** 62.
46. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. *Centre for Health Economics, University of York, Working Papers* 1999.
47. Ara R, Brazier JE. Populating an economic model with health state utility values: Moving toward better practice. *Value Health* 2010; **13:** 509-518.
48. Personal Social Services Research Unit. *NHS Cost Inflation Index*. https://www.pssru.ac.uk/pub/uc/uc2019//NHS-Cost-Inflation-Index.docx
49. UK Renal Registry. *UK Renal Registry 21st Annual Report – Data to 31/12/2017*. 2019. https://www.renalreg.org/wp-content/uploads/2019/05/21st_UKRR_Annual_Report.pdf
50. National Health Service. *National Kidney Care Audit, Patient Transport Survey – 2010*. 2011. https://digital.nhs.uk/data-and-information/publications/statistical/national-kidney-care-audit-patient-transport-survey/national-kidney-care-audit-patient-transport-survey-2010
51. Dunn P. *SOP 1023 - Transplant Laboratory Service User Manual*. 2019. https://www.leicestershospitals.nhs.uk/EasysiteWeb/getresource.axd?AssetID=75939&type=full&servicetype=Attachment
52. Gray NA, Zuo L, Hong D *et al.* Quality of life in caregivers compared with dialysis recipients: The Co-ACTIVE sub-study of the ACTIVE dialysis trial. *Nephrology (Carlton)* 2019; **24:** 1056-1063.
53. UK Renal Registry. *Data on File*. 2020.
54. NHS Trust Improvement NHSftN. *National Schedule of Reference Costs. Year 2017–2018*. 2018. https://improvement.nhs.uk/resources/reference-costs/

55. National Centre for Social Research (NatCen). *United Kingdom - Welsh Health Survey 2009 - Welsh Government.* . Cardiff: 2009.

56. NHS Blood and Transplant. *Transplant activity report 2019–2020*. 2020. https://www.organdonation.nhs.uk/helping-you-to-decide/about-organ-donation/statistics-about-organ-donation/transplant-activity-report/

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.