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

Addendum #1: Revised Section 6 ERG Report (post TE response)

January, 2021

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INTRODUCTION

The purpose of this addendum is to provide the updated ERG report Section 6 following edits made in response to technical engagement. Note that cross references link to the ERG report (date 12/11/2020, post FAC).

EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Data received from NHSBT

The population of interest in this appraisal, "those unlikely to receive a transplant under the existing protocols of the KOS", are a poorly defined group, with little information provided by the company on the outcomes and treatment patterns seen in NHS practice. For example, the split of dialysis modalities used in the economic model by the company was obtained from the whole waiting list population in the 21st annual UKRR report.[49]

To this end, the ERG requested data from NHSBT[53] to better inform the model. In order to operationalise the definition of "highly unlikely", the ERG requested data from NHSBT[53] where patients were grouping by their degree of sensitisation; all patients, ≥85% CRF (referring to the traditional definition of highly sensitised), and ≥99% sensitised (reflecting a group of patients highly unlikely to match to any individual kidney). The ERG would like to place on record its thanks to NHSBT for their rapid and extremely helpful responses to our queries.

Though the patient group detailed by the company suggests immunological factors other than CRF are also likely to affect a patient's chance to receive a match, the ERG believed that in the absence of a full definition or alternative data source, the data provided by NHSBT[53] for the CRF ≥99% group provide a reasonable proxy to the population of interest for this appraisal. Furthermore, the ERG believed the data to relate more to the population of interest than the figures reported by the company from the 21st annual UKRR report.[49]

6.2 Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a number of additional exploratory and sensitivity analyses, which are summarised below:

- In order to explore an ITT population for the intervention arm, the ERG implemented an analysis where a proportion of patients received imlifidase but did not go on to achieve a negative crossmatch, and consequently, did not receive a transplant. This proportion was varied within the sensitivity analysis to explore the impact on the model results.
- The ERG analysis assumes that a proportion of highly-sensitised patients in the comparator arm will receive a transplant without imlifidase treatment. Data obtained from

NHSBT[53] in the relevant patient population was used to populate this proportion, which was varied for sensitivity analysis.

- Data from NHSBT[53] revealed that not all patients on the transplant waiting list (in the whole population, and in the highly sensitised population) are receiving dialysis treatment. The ERG applied the distribution of dialysis status provided by NHSBT within the analysis for the patient group of interest (with the split of haemodialysis patients taken from the UKRR 21st Annual Report). The ERG was also unable to validate the proportions for the types of dialysis used in the company base case therefore alternative proportions obtained from Table 2.6 of the UKRR 21st Annual Report[49] were applied in sensitivity analysis.
- The ERG considered a recently-published utility study by Cooper *et al.*[44] as a better proxy to inform the utility values in the cost-effectiveness model due to the methodological quality, but also year of searches (2020 vs 2006). The ERG implemented these values for the analysis, with values taken from Li *et al.*[43] explored in sensitivity analysis.
- The ERG applied an alternative caregiver disutility with better methodological validity to haemodialysis patients, and reduced the proportion of patients expected to have a caregiver to explore the impact on the model results.
- The ERG was concerned with the high cost assigned to haemodialysis travel by ‘ambulance’ in the company’s analysis (>£200 for every 5th visit), and the effect on the ICER. The ERG considered an alternative approach by redistributing the proportion of patients from this transport to other NHS-cost incurring options.
- The ERG believed the omission of crossmatch tests following each full dose of imlifidase to be incorrect, and therefore have included the cost of crossmatch testing after every infusion of imlifidase.
- The average patient weight used by the company for the calculation of other drug costs (i.e. not imlifidase) was not taken from the clinical trials. The ERG has opted to implement the clinical trial average weight (i.e. the same as imlifidase) in order to more accurately reflect the patient population and be consistent in calculations.
- The ERG was concerned that the iBox predictive model was developed in a population with a different proportion of previous transplants compared to the population considered in the model. As previous transplant is a prognostic factor, the ERG has explored the impact of applying a relative risk to the iBox predictions.

- The ERG applied an increased cost for transplant to account for organ retrieval and transportation.
- The ERG considered that only a finite number of donor kidneys are available, and has therefore conducted a scenario analysis where the transplant is provided to patients who are not considered ‘highly-sensitised’ and thus, do not require imlifidase treatment.
- The ERG was concerned that DSA testing costs have not been captured in the model, therefore an analysis is conducted where DSA tests are applied once annually as transplant maintenance and at the time of graft loss.

6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The analyses described in Section 6.2 are described in turn within each section below. The impact on the ICER described below refers to the company’s base case ICER including the ERG corrections detailed in Section 5.2.

6.3.1 Patients receiving imlifidase but unable to progress to transplant

As discussed in Section 4.2.4 and Section 3.2.4, while imlifidase appears to be efficacious, there is uncertainty in the rate of crossmatch conversion from positive to negative. Although the rate is clearly high, one patient failed to achieve a negative FACS crossmatch (and received a transplant regardless as a negative virtual crossmatch result was achieved and clinical judgement supported the procedure), with two further patients having adverse reactions to imlifidase and were unable to receive a full dose (and subsequent transplant). As such the ERG has adapted the company’s model to allow a proportion of patients to receive imlifidase but not to undergo transplantation. As the true rate of crossmatch conversion is unknown the ERG has adjusted the proportion to receive transplant in the intervention arm by accounting for the patients who did not receive the full dose. Furthermore, in a scenario analysis, this proportion is also adjusted to account for the patient who did not achieve a negative FACS crossmatch. This resulted in a rate of transplant for the imlifidase arm of 96.3% in the ERG base case and 94.4% in a scenario analysis as opposed to the 100% in the company submission. This is consistent with the clinical findings where the high rate of crossmatch conversion was also subject to uncertainty.

Decreasing the proportion of imlifidase patients to receive a transplant from 100% to 96.3% resulted in an increase of £2,488 to the ICER (£31,971 to £34,459). Alternative proportions including the scenario to account for the failed conversion to a negative FACS crossmatch are explored in scenario analysis in Section 6.4.1.1.

6.3.2 Likelihood of receiving transplant without imlifidase

The economic model submitted by the company does not allow for any patients on dialysis to receive a transplant at any point in their lifetime. The ERG highlights concern with this approach in Section 4.2.4. In order to reflect that some (though not all) highly sensitised dialysis patients would receive a transplant without treatment with imlifidase, the ERG conducted the following additional analyses:

- Inclusion of an additional ERG comparator (‘dialysis and transplant’) where a proportion of dialysis patients receive a transplant.
- Heatmap combining the assumed proportion of dialysis patients to receive a transplant and the assumed proportion of imlifidase patients to receive a transplant.

The ERG noted that the ‘dialysis and transplant’ comparator only provides a limited comparison between the treatment arms as, due to the model coding, patients were assigned to either dialysis or transplant at Cycle 0. In practice it is expected that patients are likely to remain on dialysis prior to a suitable transplant becoming available – however, as patients cannot transition from dialysis to transplant in the model, no dialysis costs can be accrued prior to transplant to reflect the expected delay in receiving a transplant.

With this limitation in mind the ERG was able to perform the comparison using data provided by NHSBT[9] for years 2015 to 2019. The data showed that 119 transplants occurred for the ≥99% cRF group in the year 2019/2020 (the first full year of the revised KOS), with a mean of 77 transplants performed in the same patient group over the previous four years (2015/2016 - 2018/2019). As of 30 September 2020, there were 495 highly-sensitised patients with a cRF of ≥99% on the transplant waiting list. The 119 patients who received a transplant in the 2019/2020 year corresponds to 24.0% of 495 patients on the waiting list.

In reality, the ERG expects the number of transplants received in the 2019/2020 year to likely be inflated due to a backlog of highly sensitised patients who were suddenly assigned a higher weighting in 2019 as a result of the revised KOS. As such, the mean number of transplants over years 2015 to 2019 (85) was used to calculate an expected proportion of highly sensitised dialysis patients who would receive a transplant without treatment with imlifidase. This provided an annual probability of 17.2% (85/495). Due to the confines of the model structure, it was assumed that patients would remain fit enough for transplant for two years from model entry, following which they would become ineligible in keeping with clinical input to the ERG that eventually patients would become too sick to be transplanted. This provided a proportion of 31.4% of patients who could expect to receive a transplant in the comparator arm.

The ERG noted that due to the limitations of the model, the patients who undergo transplant in the comparator arm would incur slightly different costs in reality, as the rate of transplant would be effectively spread over time, as opposed to all occurring at Cycle 0 in the model. This unfortunately is a limitation of the model coding, but is not expected to radically change the results and represents, along with the duration for which patients may be able to undergo a transplant, a limitation.

Furthermore, clinical opinion to the ERG indicated that DSA monitoring is likely to be more frequent for patients who undergo an HLA incompatible transplant. Therefore, the ERG has applied DSA costs; monthly for the first 6 months, once every two months for 7-12 months and once annually thereafter following transplant for the patients receiving a transplant without imlifidase treatment. DSA costs are further discussed in Section 6.3.12.

Allowing 31.44% of dialysis patients to receive a transplant resulted in an ICER change from £31,971 to £59,335.

6.3.3 Changing the comparator to established clinical management, from dialysis

As discussed in Section 4.2.4, the company's economic model assumed all non-transplant patients receive dialysis. However, data provided by NHSBT[9] in the highly sensitised group (≥99%), showed that some patients are not currently on any dialysis treatment (77/491, 15.7%), with the remainder receiving haemodialysis (366/491, 74.5%) and peritoneal dialysis (48/491, 9.8%). Clinical input to the ERG agreed with this finding, with the explanation that a proportion of patients are listed for transplant pre-emptively – i.e. when eGFR <15 but still with enough kidney function to not require dialysis, whilst other patients are those with failing grafts who again maintain sufficient kidney function to be dialysis free, but do require transplantation (i.e. relisting).

To reflect the NHSBT data, the ERG implemented the proportions of patients to receive each dialysis modality (including no dialysis) in their base case analysis as taken from the NHSBT data. As the split of haemodialysis was not available from NHSBT, the proportion of patients assigned to hospital, satellite and home haemodialysis was obtained from the UKRR 21st Annual Report. The ERG understand it is likely that all patients may receive dialysis at some point however, particularly as patients age. It is therefore assumed that after the first two years, all patients will move to dialysis in the proportions seen in the NHSBT data (88.4% haemodialysis and 11.6% peritoneal dialysis). The ERG acknowledges this assumption (i.e. a maximum two years without dialysis) to be a limitation of the analysis however believe in the absence of data, it represents a plausible value, which can be changed based on data or expert opinion should the committee wish.

A further limitation is that as there is a lack of available data to inform overall survival for the patients not on dialysis, overall survival was assumed to follow the same trajectory as those on dialysis in the model. This assumption may result in an underestimate of the effectiveness of the comparator arm as it is likely these patients are healthier than those who are on dialysis i.e. they are earlier in the disease pathway.

Changing the comparator to reflect established clinical management represented an increase in the ICER from £31,971 to £32,828.

6.3.4 Utility values used for patients in the model

Using data from the recently published meta-analysis from Cooper *et al.*[44], and assuming 25% of patients are aged over 65 years (in line with the clinical studies), the ERG calculated that using longitudinal estimates, pre-transplant patients had a mean utility of 0.7385, which increased to 0.84 a year after transplant (the timepoint measured in the studies). For simplicity these values were used pre-/post-transplant, with age adjustments then applied throughout the model time horizon using the decrements from Table A of Kind *et al*[46].

These longitudinal values are important, as they consider the impact a transplant has had on a patient, rather than comparing values between groups who did, and did not receive transplant. This is as when comparing groups, the patients are also likely to differ in a number of other important factors (such as age, and comorbidities).

Using Cooper *et al.*[44] as the utility source resulted in an increase of £6,701 to the ICER (£31,971 to £38,672).

6.3.5 Utility values used for carers in the model

As discussed in Section 4.2.7, a carer disutility of 0.03 was applied for patients in receipt of haemodialysis. The ERG anticipated that not all haemodialysis patients would have a caregiver and so applied a caregiver utility to 90% of haemodialysis patients (rather than 100% in the company's base case), with 100% of patients explored as a scenario analysis.

Incorporating a 0.03 utility decrement to account for caregivers of haemodialysis patients results in a reduction of £541 (£31,971 to £31,431). Reducing the proportion of patients with a caregiver from 100% to 90% resulted in an increase of £38 to the ICER (£31,971 to £32,009)' to put them separately.

6.3.6 Cost of patient transport

The cost of patient ambulance transport used by the company (£219) is extremely similar to that of an emergency in NHS reference costs 2018-2019[54] (ASS02 See and treat and convey, £257), and is in reality likely to be a (shared) community ambulance. Furthermore, it is not clear other costs (such as taxis) need inflating given changes in the transport market over time to make it more competitive (such as the increase in ride hailing apps, and changes in transport patterns) – with 10 years since the data used was collected.

Due to this uncertainty and the absence of suitable costs, the has ERG redistributed the 18% from ambulance to the other NHS-incurred travel costs. Table 18 presents the proportion of haemodialysis patients assigned each mode of transport in the company analysis, and the reweighted proportions preferred by the ERG.

Table 18: Comparison of haemodialysis transport in company and ERG analyses

Transport	**Company**	**ERG**
Ambulance service vehicle	18%	0%
Hospital provided car	12%	16.7%
Hospital arranged taxi	12%	16.7%
Hospital transport vehicle	22%	30.6%
Public or private transport	36%	36%

Abreviations: ERG, Evidence Review Group

Applying the ERG’s reweighted proportions saw an increase of £5,114 to the ICER (£31,971 to £37,085). The ERG note however that this input is subject to substantial uncertainty, and further data could provide a better understanding of the true costs to the NHS of patient transport.

6.3.7 Cost of crossmatch tests

The company does not apply any costs associated with crossmatch testing in the model. The ERG has discussed concerns with this approach in Section 4.2.8.1.

In order to capture the costs of crossmatch testing for the analysis, the ERG applied a cost of £300 following each full dose of imlifidase received. The ERG was unable to find the cost of one FACS crossmatch test (FACS crossmatch tests were used in the clinical studies) alone however, the cost of one FACS test with one CDC test was reported in the literature[51] and so, to account for just one test being used, the ERG has halved this cost and implemented this in the model.

Applying crossmatch test costs within the model results in an increase of £78 to the ICER (31,971 to £32,049), though further information would be able to resolve this uncertainty.

6.3.8 Patient weight

The ERG found the company to have taken the average patient weight of 75 kg applied in the model from a Welsh study in 2009.[55] The ERG found the average weight of patients in the ‘all imlifidase’ patient group to be 69 kg and so have applied this in a sensitivity analysis for consistency with the costing of imlifidase (which uses actual patient weights). Using the average patient weight from the clinical studies resulted in an increase of £29 to the ICER (£31,971 to £31,942).

6.3.9 Survival post transplant in a highly pre-treated patient population

The ERG noted that the patient population in the highly sensitised group will potentially have worse outcomes than a ‘standard’ transplant population for four reasons:

- The increased CIT *ceteris paribus* when imlifidase is required to enable a transplant;
- The presence of antibodies against the donor kidney;
- The increased length of time these patients will likely have spent on dialysis;

- The number of patients who have had a prior transplant, compared to the iBox population on which estimates were based (and in which no coefficient is described for prior transplant).

Although it was not possible to quantify these concerns, the ERG provided a sensitivity analysis where a hazard ratio of 0.95 is applied to the post-transplant survival, to understand the importance of long-term survival. This change increased the ICER by £1,426 (£31,971 to £33,397)

6.3.10 Transplant costing

According to the NHSBT Activity report 2019/20[56] there were 3,760 organ transplants in the UK with a net expenditure of NHSBT of £79.9 million[4], which gives a crude cost per organ of £21,010. As the organ for any transplant has to be provided – including managing donor lists, liasing with families, retreiving organs, and transporting them under tight time windows, these costs should be included within the appraisal to be consistent with the NICE methods guide (the inclusion of all relevant costs and benefits). As such the ERG presented a scenario including this cost for transplant.

It should be noted that this cost is applied for any transplant (including in the comparator arm). The ERG acknowledged it is also likely that the cost per organ is not likely to be the same for all organs and donor types; as such improved estimates of cost may be helpful, if available. Including this cost increased the ICER from £31,971 to £33,583.

6.3.11 Reflecting the opportunity cost of a donor kidney

As discussed in both the CS and ERG report, donor kidneys are scarce with the waiting list evidencing that demand exceeds supply. As with the principle of cost-effectiveness where money not spent on an intervention will be spent elsewhere in the system, any kidneys not received by imlifidase patients would be received by other patients; i.e. imlifidase will not increase the number of kidneys available to transplant.

This question is one of the scope of the appraisal, and a question which is not covered by the NICE scope, or anticipated by the NICE methods guide (though the reflection of all costs and benefits might indicate that the opportunity [health] cost of the kidney be included).

In order to explore the impact of this opportunity cost, a comparison was made by the ERG of giving a kidney to an imlifidase patient vs to a patient not requiring imlifidase (who may or may not be in the >99% sensitised group). Although limited in its application, this scenario showed the use of imlifidase to be dominated; using a threshold of £30,000 per QALY the ERG found a net benefit of [redacted] / net health benefit of [redacted] QALYs.

6.3.12 DSA testing

As discussed in Section 4.2.8.5, no costs associated with DSA testing are applied within the model. Clinical advice to the ERG indicated that in HLA-incompatible transplants DSA monitoring would indeed be administered more frequently than with an HLA-compatible transplant. As imlifidase induces a negative crossmatch by depleting the antibodies, an HLA-compatible transplant can be performed. Although these antibodies are likely to rebound following transplant, clinical advice to the ERG was conflicting on whether additional DSA monitoring would be required for this population following imlifidase. The ERG was also unable to interpret the clinical outcome of HLA rebounds due to limited reporting in the CS (Section 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*
Allow a proportion of dialysis patients to receive a transplant – 31.44%	[redacted]	[redacted]	*£59,335*
Apply NHSBT proportion of dialysis modality (including not on dialysis)	[redacted]	[redacted]	*£32,828*
Utility source – Cooper et al. *(2020)*[44]	[redacted]	[redacted]	*£38,672*
Caregiver disutility source – Thomas et al. *(2015)*[45]	[redacted]	[redacted]	*£31,431*
Reduce the proportion of HD patients with a caregiver to 90%	[redacted]	[redacted]	*£32,009*
Redistribute hospital-paid dialysis travel cost	[redacted]	[redacted]	*£37,085*
Apply crossmatch test cost per imlifidase dose	[redacted]	[redacted]	*£32,049*
Change average patient weight to 69 kg	[redacted]	[redacted]	*£31,942*
*Apply HR to iBox graft estimates – 0.95**	[redacted]	[redacted]	*£33,397*
*Apply alternative transplant cost - £21,000**	[redacted]	[redacted]	*£33,583*

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
*Change comparator to 'Non-sensitised transplant'**	[redacted]	[redacted]	*Dominated*
Include DSA test costs	[redacted]	[redacted]	*£32,344*
ERG base case	[redacted]	[redacted]	*£98,496*

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

Note:

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

* Not included in the ERG base case

6.4 ERG's preferred assumptions

The ERG's preferred base-case analysis comprises several alternative model settings and assumptions:

1. Application of 96.3% of patients administered imlifidase to receive a subsequent transplant compared to 100% in the company's base case (Section 6.3.1).
2. Allow 31.44% of dialysis patients to receive a transplant compared to 0% in the company's base case (Section 6.3.2).
3. Application of the dialysis status distribution reported by NHSBT. Most notably this allows a proportion of patients in the comparator arm to receive no dialysis (Section 6.3.3).
4. Implement utility values taken from Cooper *et al.*[44] (Section 6.3.4).
5. Implement caregiver disutility from Thomas *et al.*[45] (Section 6.3.5).
6. Apply caregiver disutility to 90% of haemodialysis patients compared to 100% in the company's base case (Section 6.3.5).
7. Redistribute the distribution of hospital-paid transport to exclude 'ambulance' (Section 6.3.6).
8. Include the cost of one crossmatch test following each full dose of imlifidase (Section 6.3.7).
9. Use the average patient weight obtained from the clinical trials throughout the model (Section 6.3.8).
10. Include the cost of DSA test (three antigens) annually for transplant patients and at time of graft loss (Section 6.3.12).

11. 6.4.1 Summary of ERG's base case settings and assumptions

Despite the limitations highlighted within the company's model, the ERG determined a set of preferred settings and assumptions that are believed to represent a more plausible estimate of the cost-effectiveness of imlifidase. However, the ERG emphasised that several preferred assumptions such as the proportion of dialysis patients who were likely to receive a transplant without imlifidase and the amount of time comparator patients spend receiving no dialysis remain uncertain due to either model or knowledge limitations.

The ERG's preferred model settings and assumptions are summarised in Table 20. The individual and cumulative impact of each setting on the estimated ICER is presented alongside each change. The results presented are aligned with the base case results provided by the company, including equivalent settings.

Table 20: ERG's preferred model assumptions

Preferred assumption	**Section in ERG report**	**Individual change to corrected ICER £/QALY**	**Cumulative ICER £/QALY**
Company base case	*Section 5.1.1*	-	*30,641*
Company base case following ERG corrections	*Section 5.2*	-	*31,971*
Reduce the proportion of imlifidase patients to receive transplant – 96.3%	*Section 6.3.1*	*34,459*	*34,459*
Allow a proportion of dialysis patients to receive a transplant – 31.44%	*Section 6.3.2*	*59,335*	*64,592*
Apply NHSBT proportion of dialysis modality (including not on dialysis)	*Section 6.3.3*	*32,828*	*65,468*
Utility source – Cooper et al. *(2020)*[44]	*Section 6.3.4*	*38,672*	*79,558*
Caregiver disutility source – Thomas et al. *(2015)*[45]	*Section 6.3.5*	*31,431*	*80,971*
Reduce the proportion of HD patients with a caregiver to 90%	*Section 6.3.5*	*32,009*	*80,728*
Redistribute hospital-paid dialysis travel cost	*Section 6.3.6*	*37,085*	*87,349*
Apply crossmatch test cost per imlifidase dose	*Section 6.3.7*	*32,049*	*87,497*
Change average patient weight to 69 kg	*Section 6.3.8*	*31,942*	*87,462*

Preferred assumption	Section in ERG report	Individual change to corrected ICER £/QALY	Cumulative ICER £/QALY
Include DSA test costs	*Section 6.3.12*	*32,344*	*87,920*

Abbreviations: DSA, donor-specific antibodies; ERG, Evidence Review Group; HD, haemodialysis; ICER, incremental cost-effectiveness ratio; kg, kilogram; NHSBT, National Health Service Blood and Transplant; QALY, quality adjusted life year.

A comparison of the company's base case analysis and the ERG's preferred analysis results are presented in Table 21. The equivalent results of PSA using the ERG preferred assumptions are also provided.

Table 21: Comparison of company and ERG results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company original base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*30,641*
ERG base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*87,920*
Company original base case (probabilistic)							
Imlifidase	[redacted]	-	[redacted]		-		
Dialysis	[redacted]	-	[redacted]	[redacted]	-	[redacted]	*31,948*
ERG base case (probabilistic)							
Imlifidase	[redacted]	-	[redacted]		-		
Dialysis	[redacted]	-	[redacted]	[redacted]	-	[redacted]	*89,999*

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year

Note: It was not possible to obtain LY results from the cost-effectiveness model

6.4.1.1 ERG scenario analyses

A comparison of the company's scenario analyses using the ERG's preferred assumptions versus the company's base case is provided in Table 22.

Table 22: Comparison of company and ERG scenario analysis results

Scenario	ICER (£/QALY)	
	Company	**ERG**
Base-case	*30,641*	*87,920*
Company scenario analyses		
Annual discount rate (costs and outcomes) - 1.5%	*22,163*	*64,533*
Time horizon – 10 years	*62,857*	*209,605*
Time horizon – 20 years	*35,676*	*111,198*
Utility source – Li *et al.* (2017)[43]	*37,612*	*90,519*
Graft loss extrapolation – All imlifidase patients	*29,253*	*85,617*
Graft loss extrapolation – 'Unlikely to be transplanted' patients	*29,556*	*86,243*
OS with a functioning graft – 'Unlikely to be transplanted' patients	*46,896*	*187,808*
No caregiver disutility	*31,012*	*85,607*
Caregiver disutility source – Gray *et al.* (2019)[52]	*29,036*	*91,136*
ERG scenario analyses		
Account for 51/52 patients achieving a negative FACS crossmatch (proportion of imlifidase patient to receive a transplant – 94.4%)	*34,442*	*91,513*
Proportion of imlifidase patients to receive a transplant – 90%	*37,821*	*101,062*
Proportion of imlifidase patients to receive a transplant – 99%	*31,294*	*83,029*
Proportion of dialysis patients to receive a transplant – 5%	*33,727*	*54,617*
Proportion of dialysis patients to receive a transplant – 10%	*37,269*	*59,350*
Proportion of dialysis patients to receive a transplant – 20%	*45,681*	*70,678*
Use UKRR distribution of dialysis modalities	*33,771*	*85,437*
Proportion of haemodialysis patients with a caregiver – 100%	*30,641*	*88,185*
Apply HR to iBox graft estimates – 0.90	*33,605*	*93,968*
Apply HR to iBox graft estimates – 0.95	*32,036*	*90,768*
Apply alternative transplant cost - £21,000	*32,354*	*90,015*
Change comparator to 'Non-sensitised transplant'	*Dominated*	*Dominated*
Change OS dialysis source – ERA-EDTA	*33,819*	*81,137*

Key: ERA-EDTA, European Renal Association – European Dialysis Transplant Association; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life-year;

Figure 3 presents a heat map showing the effect on the company's base case ICER (without ERG correction) when the proportion of patients to receive a transplant in the intervention and comparator arms is varied. The company's base case, 100% imlifidase patients to receive transplant, 0% comparator to receive transplant, is highlighted on the figure.

Figure 3: Heat map of the company's base case assumptions varied by the proportion to receive transplant in each arm

Proportion of dialysis patients who receive a transplant \ Proportion of imlifidase patients who receive a transplant	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%
0%	$\boxed{31k}$	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 imlifidase patients who receive a transplant (columns) / *Proportion of dialysis patients who receive a transplant* (rows)

	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 ERG's base case, 96.3% imlifidase patients to receive transplant, 31.4% comparator to receive transplant, is highlighted on the figure.

Figure 5: Heat map of the ERG's base case assumptions varied by the proportion to receive transplant in each arm

Proportion of imlifidase patients who receive a transplant (columns); *Proportion of dialysis patients who receive a transplant* (rows)

	100%	99%	98%	97%	96%	95%	94%	93%	92%	91%	90%
0%	47k	48k	49k	50k	51k	52k	52k	53k	54k	55k	56k
1%	48k	49k	50k	51k	51k	52k	53k	54k	55k	56k	57k
2%	49k	50k	50k	51k	52k	53k	54k	55k	56k	57k	58k
3%	50k	50k	51k	52k	53k	54k	55k	56k	57k	58k	59k
4%	50k	51k	52k	53k	54k	55k	56k	57k	58k	59k	60k
5%	51k	52k	53k	54k	55k	56k	57k	58k	59k	60k	61k
6%	52k	53k	54k	55k	56k	57k	58k	59k	60k	61k	62k
7%	53k	54k	55k	56k	57k	58k	59k	60k	61k	62k	63k
8%	54k	55k	56k	57k	58k	59k	60k	61k	62k	63k	64k
9%	55k	56k	57k	58k	59k	60k	61k	62k	63k	64k	66k
10%	55k	57k	58k	59k	60k	61k	62k	63k	64k	65k	67k
11%	56k	57k	59k	60k	61k	62k	63k	64k	65k	67k	68k
12%	57k	58k	60k	61k	62k	63k	64k	65k	67k	68k	69k
13%	58k	59k	61k	62k	63k	64k	65k	66k	68k	69k	70k
14%	59k	60k	62k	63k	64k	65k	66k	68k	69k	70k	72k
15%	60k	61k	63k	64k	65k	66k	68k	69k	70k	72k	73k
16%	61k	63k	64k	65k	66k	67k	69k	70k	71k	73k	74k
17%	62k	64k	65k	66k	67k	69k	70k	71k	73k	74k	76k
18%	64k	65k	66k	67k	69k	70k	71k	73k	74k	76k	77k
19%	65k	66k	67k	68k	70k	71k	73k	74k	76k	77k	79k
20%	66k	67k	68k	70k	71k	72k	74k	75k	77k	79k	80k
21%	67k	68k	70k	71k	72k	74k	75k	77k	78k	80k	82k
22%	68k	70k	71k	72k	74k	75k	77k	78k	80k	82k	83k
23%	69k	71k	72k	74k	75k	77k	78k	80k	81k	83k	85k
24%	71k	72k	74k	75k	77k	78k	80k	81k	83k	85k	87k
25%	72k	73k	75k	76k	78k	80k	81k	83k	85k	87k	88k
26%	73k	75k	76k	78k	80k	81k	83k	85k	86k	88k	90k
27%	75k	76k	78k	79k	81k	83k	84k	86k	88k	90k	92k
28%	76k	78k	79k	81k	83k	84k	86k	88k	90k	92k	94k
29%	78k	79k	81k	83k	84k	86k	88k	90k	92k	94k	96k
30%	79k	81k	82k	84k	86k	88k	90k	92k	94k	96k	98k
31%	81k	82k	84k	86k	88k	90k	92k	94k	96k	98k	100k
32%	82k	84k	86k	88k	89k	91k	93k	96k	98k	100k	102k
33%	84k	86k	87k	89k	91k	93k	95k	98k	100k	102k	105k
34%	86k	87k	89k	91k	93k	95k	98k	100k	102k	104k	107k
35%	87k	89k	91k	93k	95k	97k	100k	102k	104k	107k	109k

6.5 Conclusions of the cost-effectiveness section

The work performed by the ERG addresses several shortcomings in the company submission. Although the model calculations were mostly accurate (with corrections having small influences on the ICER), the model omitted to include the appropriate application of the intervention (via an ITT approach) and the appropriate comparator. Other changes to parameters included using appropriate quality of life data, and accounting for missing costs.

Although the ERG's base case ICER increased substantially, this was almost entirely due to reflecting the decision problem, reflecting that not all imlifidase patients achieve transplant and not all standard care patients fail to achieve transplant. For completeness, changing only these two items increased the ICER from the company's base case of £30,641 to £63,585; with correcting costing and other issues (such as utilities) accounting for the remaining increase to £87,920 which represents the ERG's base case.

The findings of sensitivity and scenario analysis further demonstrated the importance of understanding the opportunity cost of kidneys (which leads to imlifidase being dominated, a loss of [redacted] QALYs to the health care system using a £30,000 threshold and the company's uncorrected assumptions). Other important factors included the survival of patients (which the ERG was unable to adequately assess given the data used), and utility values used (which are uncertain due to being taken from the literature, and not the specific population). The remaining issue the ERG noted was the structural uncertainty present in the model. Although the company model with the ERG base case represents a reasonable estimation given the information available, there exists uncertainty in how imlifidase would be used in practice, what the survival of patients would look like, and their quality of life (as no data was captured in the clinical trial). Although not able to be included in the model, these are uncertainties that the ERG would highlight.