NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease [ID1672]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease [ID1672]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.
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1. **Response to consultee, commentator, and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from** Hansa Biopharma

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. British Transplantation Society
   b. UK Kidney Association
   c. NHS England and NHS improvement

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Hansa	**Executive Summary: Hansa ACD Response** 1. **Has all of the relevant evidence been taken into account?** o The imlifidase 3 year follow up trial data is robust, relevant and should not be disregarded for appraisal decision making purposes. The efficacy and safety of imlifidase are consistent, irrespective of the subgroup imlifidase enables the transplantation. See Comment Number 10 o The Post Approval Efficacy and Safety (PAES) study and its potential for UK data collection should not be disregarded for this appraisal, particularly as Guy's, Leeds and UHCW have already been selected as PAES study trial centres. See responses in See Comment Number 16 2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** o Hansa engaged and gathered feedback from 15 HLAi clinical experts in eight transplants centres across England, Wales and Northern Ireland to ensure that committee recommendations were in line with NHS clinical practice of kidney transplantation for highly sensitised patients. Feedback received is incorporated into this response. o The potential risk of longer cold ischaemia time (CIT) and the potential consequence of organ wastage is overestimated and needs to be put in the appropriate clinical context. The Committee's recommendation rests on the concern that imlifidase use leads to unacceptable CITs and organ wastage. Hansa disputes this, on the basis of imlifidase clinical trial data which shows no kidneys were discarded due to CIT, or for any other reason. The trial data also shows that nearly all patients will only require one imlifidase infusion and rigorous selection of recipients and donors in line with proposed eligibility criteria, as well as appropriate delisting of antigens should further negate the need for a second imlifidase infusion. In addition, all transplant experts we have spoken to indicated that although they acknowledge that imlifidase will lengthen CIT in most cases, this is not a barrier for use on imlifidase See Comment Number 8 o The rates of AMR seen across imlifidase clinical trials are in line with what is expected in the proposed population and HLA incompatible kidney transplantation. See Comment Number 11	Comment noted. Thank you for stating your position. The committee carefully considered these issues raised along with feedback from other consultees in its decision-making at the third Appraisal Committee Meeting.

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			3. **Are the recommendations sound and a suitable basis for guidance to the NHS?** ○ Imlifidase is an innovative technology that provides substantial and distinctive benefits that may not be captured by measuring health gains such as providing hope for a group of patients that currently have no hope of receiving a transplant. Therefore, the Committee's recommendation is not aligned with NICE Principle 8. See Comment Number 3 ○ The committee's concerns regarding the opportunity cost for non-sensitised patients are not in keeping with the principles of the KOS which is designed to balance equity and utility. Deceased donor (DD) kidneys are a finite resource, and any future imlifidase patient is already part of the pool of patients waiting for this finite resource, and as such should be treated equitably, based on their position on the waiting list and therapeutic options available. The negative impact for non-sensitised patients is a delayed kidney transplantation (by a few days to a few weeks), not a denied kidney transplantation. Whereas imlifidase enables transplantation of patients who currently have no chance of kidney transplantation, despite recent changes in the Kidney Offering Scheme (KOS). Therefore, the committee's recommendation is not aligned with NICE Principle 9. See Comment Number 9 and 12 4. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** ○ Imlifidase is a step-change in treatment in deceased donor kidney transplantation. implementation should not be a barrier for providing patients an innovative treatment option such as imlifidase, and whose only option is to remain on long-term dialysis which has a significant negative impact on healthcare costs, morbidity, mortality and quality of life. Therefore, not recommending imlifidase does not align with NICE principle 8. See Comment Number 15 ○ NHSBT modelling suggests that the changes to the KOS will improve but never completely resolve the inequity of access for highly sensitised patients. Therefore by not recommending imlifidase, an opportunity is removed to help improve equity of access to kidney transplant for female and highly sensitised patients, which is not aligned with *NICE Principle 9 … our guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged. See Comment Numbers 12 and 14*	

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2	Company	Hansa	**ACD Section 1 – Why the Committee made these recommendations – PRIORITY RESPONSE** • **ACD Statement: "**The clinical evidence was limited and had a short follow up. There is a lack of long term evidence to show the benefits of imlifidase." **Hansa response:** For further information see Comment Number 10 • **ACD Statement: "**Using imlifidase might substantially increase the time from a kidney being donated to the transplant taking place." **Hansa response:** For further information see Comment Number 8 • **ACD statement: "**The changes to the UK Kidney Offering Scheme in 2019 have improved access for people who are highly sensitised to HLA. These people might now have improved access to a suitable matched kidney without imlifidase." **Hansa response:** For further information see Comment Number 12	Comment noted. A final appraisal document has now been produced, recommending imlifidase with certain conditions. The section relating to 'Why the committee made these recommendations' has since been updated following the committee discussions at the third Appraisal Committee Meeting.
3	Company	Hansa	**ACD Section 3.1 Renal replacement therapies while waiting for a kidney transplant can have a substantial effect on quality of life** • **ACD statement:** "The committee recognised that people who are on dialysis, especially for a long time while waiting for a kidney transplant, have reduced quality of life. These people would prefer a transplant if a suitable donor kidney was available." **Hansa response:** Imlifidase is an innovative technology that provides substantial and distinctive benefits that may not be captured by measuring health gains such as providing hope for a group of patients that currently have no hope of receiving a transplant. Therefore the committee's recommendation goes against NICE M 8 *NICE aims to support this innovation by encouraging interventions that provide substantial distinctive benefits that may not be captured by measuring health gain (that is, the estimated QALYs gained).* Additionally, this statement does not fully reflect the feedback provided by the Kidney Research UK statement at the 2nd Committee Meeting and the true burden of dialysis: "If I was a dialysis patient knowing I would never have a transplant and never get away from dialysis I would feel life was pretty pointless, particularly as I got older and probably had secondary heath issues. I think I would feel futile, angry and I am sure thoughts of suicide might even play on my mind. Transplant gives opportunity for longer, healthier and potentially more fulfilling life. But all hope can be stolen if you are told you can't have a transplant because it will be rejected." Dialysis impacts patient lives every day in a significant way. Dialysis drives patients' day to day (diet, fluid intake, dialysis procedure itself), and hinders their ability to live their lives as they want to (holidays, family planning, etc.) These daily constraints have a profound impact on patients' mental health and wellbeing. According to clinicians and patient associations we have spoken to, many fully informed patients are willing to accept a higher level of transplant risk in order to be able to once again experience life without having to be tethered to dialysis three times every week, even for a short period of dialysis-free time. And only having hope that a transplant might be possible may change their life outlook significantly.	Comment noted. The committee carefully considers the views of patient experts in its decision making. This statement was originally included in the ACD but has been amended in the FAD.

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4	Company	Hansa	**ACD Section 3.2. People who are highly sensitised wait longer for a suitable donor kidney than those who are not sensitised** • **ACD statement:** "This is because this creates the opportunity of either directed donation transplant or transplant through the UK Kidney Living Kidney Offering Scheme." **Hansa response:** Correction required: amend "Living Kidney Offering Scheme" to "UK Living Kidney Sharing Scheme" or "Kidney Offering Scheme", as appropriate • **ACD statement:** "Since 2019, the number of people in this group getting transplants has increased (see Comment Number 8). The committee concluded that before this change, people who are highly sensitised waited much longer on average for a kidney transplant from a deceased donor, compared with people who are not sensitised." **Hansa response: Please see response for See Comment Number 12 for further information**	Comment noted. Thank you for highlighting this. This text has been corrected to 'Kidney Offering Scheme' in the FAD. Comment noted. Following the committee discussions at the third Appraisal Committee Meeting the conclusion has been updated. Please see section 3.2 in the FAD.
5	Company	Hansa	**ACD Section 3.3. People who have waited a long time for a transplant may not be well enough to have one by the time a suitable donor is found** • **ACD statement:** "Or they may attempt to use a novel desensitisation approach like plasma exchange to remove the HLA antibodies." **Hansa response:** Desensitisation protocols such as plasma exchange are of variable efficacy and take weeks to complete. They are therefore not an option for a deceased donor transplantation in HS patients, which is the indication for imlifidase.	Comment noted. Thank you for highlighting. This text has been removed from the FAD.
6	Company	Hansa	**ACD Section 3.4 Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people** • **ACD statement:** "Some people who had imlifidase in the trials also had a more intensive regimen of immunosuppression drugs after transplant than is currently used in the NHS for transplants without imlifidase. The committee concluded that imlifidase could give some people who are highly sensitised access to a kidney transplant sooner, but that some of these people may need more intense immunosuppression afterwards." **Hansa response:** Post-transplant immunosuppression is standard practice for UK centres offering HLAi transplantation in the UK. The difference between UK and Swedish/US clinical practice was not considered to be a valid reason to prevent patients receiving imlifidase in initial study visits for Guy's, Leeds and UHCW which are the UK centres in the imlifidase PAES study. Importantly, although some of the imlifidase patients will require a more intensive immunosuppression regimen, the alternative for these patients is to remain on dialysis indefinitely which has substantial morbidity, mortality and quality of life impacts.[i]	Comment noted. The committee hast taken this into consideration. Following the committee discussions at the third Appraisal Committee Meeting this section has been amended. Please see section 3.4 of the FAD.
7	Company	Hansa	**ACD Section 3.5. The proposed population might be appropriate but needs to be considered in the context of current NHS clinical practice** **ACD statement: "**They noted that the proportion of deceased donor kidney transplants	Comment noted. This information has been updated in the FAD. Where appropriate we have cross-referred to the relevant sections for clarity.

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			going to people with a CRF of 100% had doubled from 2% to 4% in the first year of applying the new UK algorithm and this showed evidence that patients are doing better since the criteria was changed. But, despite this there are still people who would only be able to have a transplant if imlifidase were to become available." **Hansa response:** To ensure consistency throughout the ACD, we recommend this statement is added into ACD Sections 1. 3.2, 3.11 where it is stated that the current KOS has increased the number of highly sensitised patients getting transplants "But, despite this there are still people who would only be able to have a transplant if imlifidase were to become available." For further information please see Comment number 12	
8	Company	Hansa	**ACD Section 3.6. The proposed treatment pathway likely underestimates the impact on cold ischaemic time of the donor kidney – PRIORITY RESPONSE** • **ACD statement:** "In that pathway, the estimated cold ischaemic time varied between 10 to 24 hours, depending on the number of imlifidase infusions and number of crossmatch tests needed." **Hansa response:** This statement does not quantify how unlikely it is for the CIT to reach the upper bounds of this range in imlifidase-enabled transplantation. In imlifidase clinical trials, 93.5% (43/46 patients) of imlifidase enabled transplants had a crossmatch conversion after 1 dose. Of the patients that required two imlifidase infusions, [redacted] Rigorous selection of recipients and donors in line with proposed eligibility criteria, as well as appropriate delisting of antigens should further negate the need for a second imlifidase infusion. The ERG's proposed pathway uses 6 hours as the turnaround time for a crossmatch test. Centres which we have spoken to say that they have labs on site, and that the turnaround time could routinely be as low as 2-4 hours. There are also scenarios whereby imlifidase-enabled transplants can be performed without any increase in the CIT whatsoever. Such an instance is set out in the schematic below, as constructed by Professor Briggs, Director, H &I Lab, NHSBT, Birmingham	Comment noted. Thank you for providing this detail. The committee considered this as well as information provided by other consultees. It further discussed the impact of cold ischaemic time at the third Appraisal Committee Meeting. Please see section 3.6 of the FAD for the committee considerations.

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			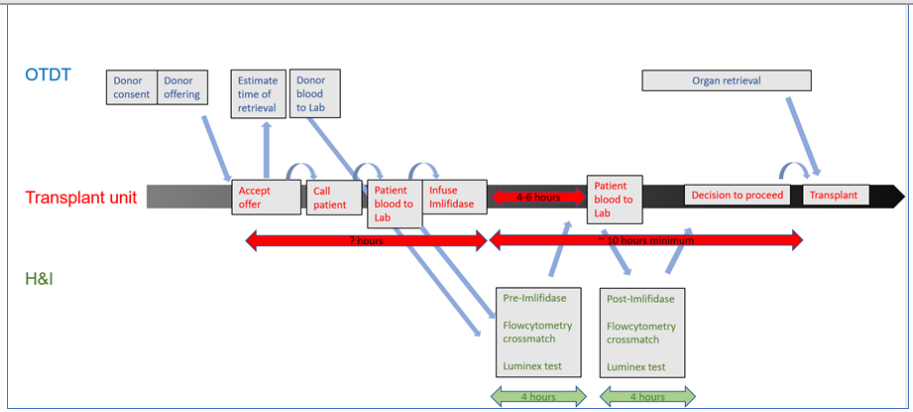 • **ACD statement:** "A time of more than 24 hours would mean the donated kidney effectively becomes unusable for transplant." **Hansa statement:** This statement is inaccurate. UK clinicians consulted have reported that they regularly transplant kidneys with a CIT of 24 hours or over. Kidneys do not become automatically unusable past the 24-hour mark. [ii] The NHSBT annual report states "Evidence indicates that the outcome is only adversely effected when CIT is longer than 20 hours, although many deceased donor transplants with a CIT of more than 20 hours have been very successful."[iii] In the most recent NHSBT Annual Report on Kidney Transplantation, [3] it is shown that though CIT has fallen a little over the years, transplants are still being performed with over 24 hours CIT. See graph below.	Comment noted. Thank you for providing this data. This information has now been updated in the FAD. Please see section 3.6 of the FAD.

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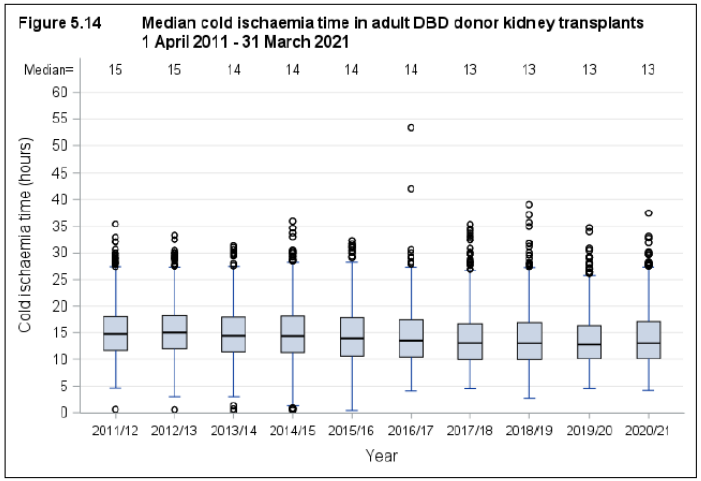
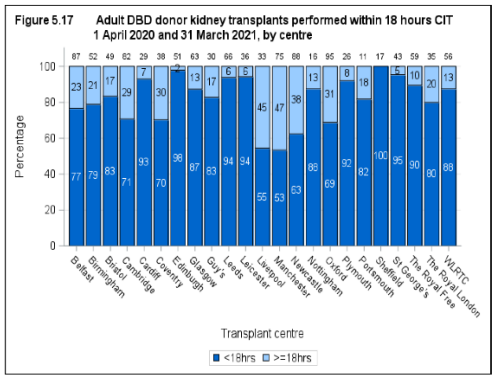
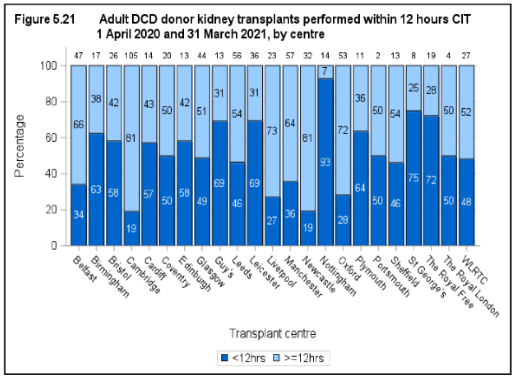
			 The NHSBT Annual Report[3]also shows there is considerable variation across centres in the proportion of adult DBD kidney transplants that have been performed within 18 hours of CIT. Indeed, there are centres where almost 50% of transplants surpass this threshold.   • **ACD Statement:** "The clinical experts said that the potential of a second imlifidase infusion would add an unacceptable amount of time to the life of the kidney." **Hansa response:** This was not the view shared by the clinicians Hansa consulted at 8	Thank you for providing this detail. The

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			transplants centres across the UK. In relation to the imlifidase clinical trial data, no kidneys were discarded due to CIT (despite the mean total CIT in the 3 year follow data being [redacted] hours which includes organ retrieval and transport to the transplanting hospital), or for any other reason, in the imlifidase clinical trials. In addition, the Post Approval Efficacy and Safety study is planned to be conducted at 3 centres in the UK: Guy's, Leeds and UHCW. Initial study visits have taken place at all these sites and none of the clinicians involved have raised concerns that a second infusion would increase the CIT to an unacceptable time period. The transplant MDT will continually assess the benefits and risks of proceeding with the transplantation, including the CIT as well as many other variables. If the imlifidase-enabled kidney transplantation cannot take place due to an excessive CIT, the kidney will not be discarded. NHSBT have a mechanism called the Fast Track Scheme which is designed to optimise the utilisation of kidneys available for transplantation through simultaneous offering to previously declined, difficult to place kidneys to a number of centres who had opted in to receive such offers. It would be possible for NHSE&I to implement more measures to further minimise this risk, such as the provision of a backup patient. This will be for NHSE&I to decide with NHSBT and the potential imlifidase MDT.	committee took this into consideration at the 3rd Appraisal Committee Meeting. Its discussions are reported in section 3.6 of the FAD.
			• **ACD statement:** "Centres used in the clinical trial were not based in the UK and the committee acknowledged there could be important differences between these centres and NHS practice which could lead to differing cold ischaemic times. These centres might have been well placed for short cold ischaemic times, by providing high numbers of transplants and donors close-by. But The committee had not seen evidence that a similar result could be achieved in UK clinical practice." **Hansa statement:** As indicated by numerous clinical experts, including three of the NICE clinical experts in their statements, the results from the imlifidase clinical trials can readily be extrapolated to the UK setting. Careful selection of donors, recipients and transplant centres, as well as refining the treatment pathway at the designated imlifidase centres can considerably help optimise results from imlifidase-enabled transplants. A consideration from the study data is the difference in CIT between DD patients from the US and those from Europe. See table below. In Europe, all DD patients were transplanted in Sweden. In this Swedish cohort there were no occurrences of delayed graft function. As might be expected, largely for geographical reasons, [redacted]. For the UK, we would expect the better comparator cohort be the EU/Swedish cohort. It is worth clarifying that CIT calculated in our clinical trial started at organ retrieval and included transport to transplanting hospital.	Thank you for providing this data. This was considered by the committee.

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<tr><td>EU (n=[redacted])</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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ACD statement: “Treatment would likely be focused in 4 specialist centres across the country but would need a tendering process to establish which centres could be involved.”
Hansa response: CIT for an imlifidase-enabled transplantation will be further managed as a result of the NHSE&I suggestion of choosing specialist centres which have robust and efficient protocols in place for cross-match testing and on-site laboratories. We look forward to further working with NHSE&I and clinicians on this topic
</td><td>Comment noted. Thank you.</td></tr>
<tr><td>9</td><td>Company</td><td>Hansa</td><td>
ACD Section 3.7. Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised – PRIORITY RESPONSE
ACD statement: “The committee recognised that the opportunity created by ensuring people who are highly sensitised are treated equally and fairly would need to outweigh any additional costs and any benefit loss created for people who are not highly sensitised, to reflect all costs and benefits.”
Hansa response: This statement also goes against NICE Principle 9: Aim to reduce health inequalities. Hansa disagrees that the equity benefit for highly sensitised patients should outweigh the benefits loss for those who are non-sensitised. The current KOS is not designed to maximize utilities, rather to balance equity and utility. Deceased donor (DD) kidneys are a finite resource, and it is universally true that when any patient receives a DD kidney, there is another patient who doesn’t and remains on the waiting list. Any future imlifidase patient is already part of the pool of patients waiting for this finite resource, and as such should be treated equitably, based on their position on the waiting list and therapeutic options available. The concept of maximizing health benefits in kidney transplantation in NHS was recently researched and published. The authors came to the conclusion that “This approach (QALY maximation) yielded the most QALYs for transplant recipients but also resulted in a notable decrease in access to transplantation for older patients. Although the QALY maximization approach made more efficient use of a limited number of kidneys, it resulted in greater inequity in terms of both access to transplantation and the distribution of QALYs between transplant recipients and patients who remained on the waiting list” [iv]
Implementation of imlifidase would align with the KOS objectives as the proposed eligible population is already prioritised by the KOS (as they have Tier A status). See Comment Number 12 for further information.
In addition, the concept of opportunity cost would in this case mean a comparator outside the imlifidase licensed indication, namely non-sensitised patients, and therefore should not
</td><td>Comment noted. The committee is mindful of the principles that guide the development of NICE guidance and standards and has discussed this issue further at the 3rd Appraisal Committee Meeting. These discussions are reported in section 3.8 and 3.16 of the FAD.</td></tr>
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			be assessed within this NICE technology appraisal. • **ACD Comment: "**Stakeholders explained that any donor kidney used with imlifidase could have been used for someone else with much lower costs, better outcomes and equal related savings from avoiding dialysis. Because the clinical and cost effectiveness would be lower for some transplants using imlifidase, this could result in a loss of health benefit and increased costs overall for the healthcare system. " **Hansa response:** Imlifidase enables equity of access to kidney transplantation for a small subgroup of patients (see response to section 3.11) who demonstrate graft survival outcomes similar to other patient populations routinely transplanted (e.g. diabetics, FSGS, IgA nephropathy).[v] If the opportunity cost drove decision-making in transplantation, such patients, as well as smokers and elderly patients, would no longer be transplanted. This would go against NICE Principle 9. ○ **ACD Statement: "**Any decision should take account of the opportunity cost that the kidney will be unavailable for other people on the waiting list who are not sensitised**."** **Hansa response:** Non-sensitized patient not receiving a kidney transplant in this situation will likely only experience several weeks delay in kidney transplantation and certainly would not be denied kidney transplantation altogether. By contrast, an imlifidase transplant is the only route to enable transplantation for a small subset of patients with no alternative other than long-term dialysis with substantial morbidity, mortality and quality of life impact.[1] To help quantify this point we have roughly estimated the time it would take for a subsequent offer to be received for a non-imlifidase patient. The latest NHSBT activity report shows that in the year ending April 2021, the median waiting time for a kidney transplant in the UK was 633 days. There were a total of 3,525 patients on the waiting list on 31/3/2021, and in the year ending March 2021 1,790 DD kidney transplants were carried out. Assuming that in the same year [redacted] patents had been transplanted with imlifidase, the impact for the next patient matched to the same organ would be, on average 3.5 days (10 / 1,790 = 0.56%, 633 x 0.56%) = 3.5 days. This should be rounded up to 1 or 2 weeks to account for variation in daily transplantations. By contrast, those patients receiving a transplant with imlifidase would previously have had, little to no prospect of a transplant.	Comment noted. Thank you for providing this data. The committee further discussed this issue at the third Appraisal Committee Meeting. This section of the ACD has now been updated. The discussions are documented in section 3.8 of the FAD.
10	Company	Hansa	**ACD Section 3.8. The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS (cf similar drugs for rare diseases) – PRIORITY RESPONSE** • **ACD statement: "**The ERG considered that the quality of data beyond the original trials was limited." **Hansa response:** The imlifidase 3 year follow up trial data is robust, relevant and should not be disregarded for appraisal decision making purposes. The indication for this appraisal is classed as rare therefore the trials are consequently small in numbers. Imlifidase was studied in 46 transplanted patients, which for Phase 2 development in	Comment noted. The committee considered all the evidence submitted, as well as considering additional stakeholder comments regarding the relevance of the data. It discussed this issue further at the third Appraisal Committee Meeting and has revised its conclusions. These discussions are reported in section 3.9 of the FAD.

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			orphan diseases is by no means limited. The significant unmet medical need in our licensed indication supported EMA's decision to grant a conditional marketing authorisation based on this same Phase 2 data. Hansa recognizes that the evidence pack will be further strengthened when the Phase 3 PAES study is conducted (including 3 UK centres). However, the efficacy and safety of imlifidase were deemed enough to grant conditional marketing approval, and the indicated patients currently have no access to kidney transplantation and their only prospect is to remain on long term dialysis which has a significant negative impact on healthcare cost, mortality and quality of life.[1] Our 3-year data published last year is in fact the longest-term clinical trial data in the area of highly sensitised kidney transplantations.[vi] This makes our trial data highly relevant, extremely important and not to be disregarded for appraisal decision purposes. At the time of HTA decision it is not uncommon to only have 3 years of follow up data available. The uncertainty is diminished by the fact that the efficacy and safety of imlifidase are consistent, irrespective of the subgroup imlifidase enables the transplantation.	
11	Company	Hansa	**ACD Section 3.9. Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm (cf likelihood of not receiving a transplant whatsoever) – PRIORITY RESPONSE** • **ACD statement: "**The committee considered that there was a high rate of antibody mediated rejection (40%) in the company's original clinical data." **Hansa response:**. AMR rates are higher in incompatible transplantation than in standard transplantation. This is one of the reasons that compatible transplantations are the preferred solution. For patients who cannot benefit from compatible transplantation, there are still, in most cases, substantial benefits with incompatible transplantation compared to dialysis, despite the higher AMR rates incurred. In the recently published 3-year imlifidase follow up data, the overall incidence of AMR was 38%, with the majority of these episodes taking place in the first month following transplantation.[6] None of the AMRs lead to graft failure or death. Clinicians consulted on this have consistently stated that this AMR rate is in line with what is expected in clinical practice when carrying out HLA incompatible kidney transplants, many disagreeing with the figure of 10% for occurrence of AMRs in the highly sensitised population. This figure is more aligned to the incidence witnessed in the compatible transplantation setting.	Comment noted. Thank you for providing this information. The committee considered this issue as well as considering other stakeholder responses It discussed this further at the third Appraisal Committee Meeting. Please see section 3.10 of the FAD for these updates.
12	Company	Hansa	**ACD Section 3.11. Data shows that some people for whom imlifidase might be suitable already have access to transplants – PRIORITY RESPONSE** • **ACD statement** "…and concluded that some people for whom imlifidase might be suitable will already have access to transplants." **Hansa response:** This conclusion contradicts the statement said in Section 3.5 – please see Hansa response above This conclusion also goes against NICE *Principle 9. Aim to reduce health inequalities:*	Comment noted. This section was originally included in the ACD but has not included in the FAD. The committee is mindful of the principles that guide the development of NICE guidance and standards and has further considered the eligible population in regards to the Kidney Offering Scheme at the 3rd Appraisal Committee meeting. Please see

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			…..So our guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged. The new KOS has increased chances of a transplant for highly sensitized patients as NHSBT data shows that the proportion of transplants for patients with cRF>99.5% in the UK went from 2% of total transplants performed prior to Sept 2019 (implementation of the new KOS) to 4% in the year following. However, patients with a cRF> 99.5% still currently represent approximately 10% of the waiting list. In addition, NHSBT modelling suggests that the changes to the KOS will never completely resolve the inequity of access for this patient population.[vii] These patients face the prospect of remaining on long-term dialysis which has substantial negative impact on health, cost and quality of life.[1] The proposed imlifidase eligibility criteria are aligned with this small subset of transplant patients identified in the NHS BT data as being most unlikely to be transplanted and are also prioritised within the current KOS (as they all have Tier A status).	sections 3.5; 3.8 and 3,16 of the FAD.
13	Company	Hansa	**ACD Section 3.12. Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain** • **ACD statement: "**It concluded that not everyone who has imlifidase goes on to have a kidney transplant, but the exact proportion is uncertain." **Hansa response:** The assumption accepted by the ERG and used in economic model was using the robust clinical trial data available and should not be discounted (see Comment Number 10). The uncertainty is further diminished by the fact that the efficacy and safety of imlifidase are consistent, irrespective of the subgroup imlifidase enables the transplantation.[6]	Comment noted. The committee has taken this into consideration in its discussions. These are reported in section 3.12 of the FAD.
14	Company	Hansa	**ACD Section 3.18. Specific consideration needs to be given to people who have become highly sensitised through pregnancy** • **ACD statement:** "Clinical experts noted that one of most common causes for a person to be highly sensitised with HLA is previous pregnancy." **Hansa response:** It has been demonstrated that imlifidase enables transplantation for highly sensitised patients, regardless of the cause of their sensitisation. NHS BT data clearly show that in the cohort of most highly sensitised patients, females have a lower probability of being transplanted than males, and constitute a higher proportion of this population.[7] In turn, imlifidase is currently the only treatment option to enable kidney transplantation for a small subset of highly sensitised patients such as this. Therefore, not recommending imlifidase goes against NICE *Principle 9. Aim to reduce health inequalities: …..So our guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged.*	Commenty noted. Thank you for highlighting this information from NHSBT. The committee is mindful of the principles that guide the development of NICE guidance and standards and has further considered this issue at the third Appraisal Committee Meeting. Please see section 3.16 of the FAD for its conclusions.
15	Company	Hansa	**ACD Section 3.19. Imlifidase could provide a step-change in treatment but there are challenges/alterations for implementation - PRIORITY RESPONSE** • **ACD statement:** The committee concluded that imlifidase could provide a step-change in	Comment noted. Thank you for highlighting your position. The committee is mindful of the principles that guide the development of NICE guidance and

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			treatment but there are challenges for implementation. **Hansa response:** Not recommending imlifidase goes against *NICE Principle 8. Support innovation in the provision and organization of health and social care services*. Imlifidase is a step-change in treatment in deceased donor kidney transplantation, and when Hansa consulted with UK clinical experts across the country, the potential challenges in its implementation are considered to be readily manageable. Any potential implementation challenge needs to be assessed within the appropriate clinical context (see Comment Number 8). Irrespective, implementation should not be a barrier for providing patients an innovative treatment such as imlifidase which is the only option to enable transplant for a small subset of highly sensitised patients. Imlifidase has been reviewed as part of the EMA PRIority MEdicines (PRIME) programme which supports medicines that may offer a *major therapeutic advantage* for patients without treatment options. EMA identified Idefirix as an Outstanding Contribution to Public Health, awarded to only 12 medicines approved in 2020 that represent significant progress in their therapeutic area. Imlifidase was granted conditional marketing authorisation as there is a clear unmet need for a small subset of highly sensitised patients who remain unlikely to be transplanted despite the moderate success of the currently kidney offering scheme. The proposed imlifidase eligibility criteria are aligned with this small subset of transplant patients identified in the NHSBT data as being most unlikely to be transplanted and are also prioritised within the current KOS (as they all have Tier A status). The only prospect for these patients is long-term dialysis, which has a significant negative impact on healthcare costs, morbidity, mortality and quality of life.[1] See Comment Number 12	standards The committee has revised its conclusions following. The committee discussions at the third Appraisal Committee Meeting. These discussions are reported in Section 3.17 of the FAD.
16	Company	Hansa	**ACD Section 3.20. Managed access agreement is not appropriate** • **ACD statement:** It considered that the ongoing studies are unlikely to provide meaningful additional data for committee decision making. • **Hansa response:** Hansa disagrees with this statement. The Post Approval Efficacy and Safety study will collect relevant outcome (e.g. graft outcomes) and safety data (e.g. AMR and CIT) relevant to this appraisal and will be conducted in selected UK hospitals.	Comment noted. Thank you for providing this information regarding the Post Approval Efficacy and Safety study. The committee discussed the relevance of a Market Access Agreement further at the third Appraisal Committee Meeting. These discussions are reported in section 3.18 of the FAD.
17	Company	Hansa	**ACD Section 1 – Why the Committee made these recommendations - PRIORITY RESPONSE** • **ACD statement: "**The cost-effectiveness estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources." **Hansa response:** Please see comment number 19 for the current base case estimates which demonstrates that imlifidase is a plausibly cost-effective treatment options across all base case scenarios. Hansa acknowledges that this is an exceptional appraisal for the ERG and NICE committee as this the first technology appraisal in this innovative drug class within this rare indication of significant unmet need. Although it cannot be directly utilised for decision making purposes within this current appraisal, Hansa would like the committee to note that NICE have recognised this exceptionality within the proposed review of NICE methods, giving additional weight to health benefits in the most severe	Comment noted. Thank you for providing your cost effectiveness estimates. Considerations about cost effectiveness are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19. Following committee discussions at the third Appraisal Committee Meeting the section describing 'why the committee made these recommendations' has been updated.

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<tr><td></td><td></td><td></td><td>conditions, a health inequalities modifier and opportunities for handling uncertainty. In addition, Hansa would like to reiterate current NICE methods guidance regarding factors which should be specifically accounted for when assessing the effective use of NHS resources. Section 6.3.3 of the guidance outlines the following factors:

• The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure – see Comment Number 15
• Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21) – see comment number 3</td><td></td></tr>
<tr><td>18</td><td>Company</td><td>Hansa</td><td>Section 3.13. Graft survival projections from iBox are highly uncertain so a hazard ratio should be applied to account for this

• ACD Statement: “It concluded that graft-survival predictions were highly uncertain because of data from a very small data sample informing long-term extrapolations.”
Hansa response: Hansa’s base case assumption for graft survival projections remains the 3-year follow up data. We believe that this is the most relevant data set to model graft survival. Please see comments number 10 for further information on rationale for not disregarding this data set for decision making purposes.
It is widely accepted that long-term allograft survival is impacted by multiple variables including (but not limited to) medication non-adherence, donor graft quality, ischemic reperfusion injury, co-morbid conditions and original cause of kidney failure. Therefore, it is difficult to compare the potential outcomes of patients who receive an imlifidase-enabled kidney transplant to any other cohort than the true standard of care, which are patients currently awaiting a compatible organ offer while on dialysis.
Hansa does however accept that NICE needs to validate evidence sources used for decision making. Therefore, Hansa recommends the iBox graft survival extrapolation is a relevant scenario to validate the 3 year-follow up base case against. When comparing the 5-year and 10-year survival estimates from the two most recent UK data sources published (NHSBT Annual report data[3] and a paper published last summer by Krishnan et al[viii] at University Hospital Coventry and Warwickshire (UHCW) hospital on incompatible transplantations) with the iBox projections, 5-year and 10-year graft survival rates are all higher than the iBox extrapolations. It can be concluded that there is no robust rationale for applying a 0.9 hazard ratio (HR) to the iBox extrapolation. On this basis, we request that the NICE/ERG base case is updated with the 0.9 HR removed, and that the ‘3 year follow up’ scenario is factored into committee decision making.

<table>
<tr><th>Source</th><th>Five year Graft Survival</th><th>Ten year Graft Survival</th></tr>
<tr><td>NHSBT 2007-2009, DCD [3]</td><td>0.86</td><td>0.75</td></tr>
</table>
</td><td>Comment noted. Thank you for providing this data. The committee took this into consideration at the third Appraisal Committee Meeting. These have been reported in section 3.13 of the FAD.</td></tr>
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<table>
<tr><td>NHSBT 2013-2015, DCD [3]</td><td>0.86</td><td>-</td></tr>
<tr><td>NHSBT 2007-2009, DBD [3]</td><td>0.85</td><td>0.74</td></tr>
<tr><td>NHSBT 2013-2015, DBD[3]</td><td>0.87</td><td>-</td></tr>
<tr><td>Krishnan et al, 2021, HLAi cohort[8]</td><td>0.85</td><td>0.70</td></tr>
<tr><td>Imlifidase iBox</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Imlifidase iBox, HR = 90%</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>All imlifidase extrapolations – 3 year follow up data</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>UTT imlifidase extrapolations – 3 year follow up data</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td></td></tr>
<tr><td>19</td><td>Company</td><td>Hansa</td><td colspan="2">[The company provided revised cost-effectiveness analysis in response to consultation, but further updated that analyses which has superseded this and is not presented here (please see document 7]</td></tr>
<tr><td>20</td><td>Consultee</td><td>UK Kidney Association</td><td>On behalf of the UKKA, overall, I believe the provisional recommendation and guidance to be sound.

Notably:
a. Assessment of the impact of the KOS 2019 now needs to be considered in the clinical and cost effectiveness model. As a single centre, over 15% of our kidney transplant recipients transplanted since the change have a cRF>85%. It should also be considered that the full impact of the 2019 KOS probably has been hindered by the COVID pandemic during 2020 (pre-vaccination), when transplant units were closed or selective in their recipients.
b. Cost effectiveness has to include the use of additional immunosuppressive therapies, e.g IVIG and rituximab which are not routinely used in the UK.
c. The long-term outcome data for Imlifidase is not available, but early rejection in ‘HLAi’ is recognised to be associated with the development of chronic antibody mediated rejection and premature graft loss. I note the early rejection rates provided as evidence occurred in just under <50%.
d. The agent will be best assessed as part of a study to best determine its role in the UK</td><td>Comment noted. Thank you for your feedback.</td></tr>
<tr><td>21</td><td>Consultee</td><td>UK Kidney Association</td><td>The evidence review has focused on deceased organ transplant recipients alone where the overall benefit for organ utilisation will be neutral as alternatively the organ would be used in a low-risk recipient, in whom the transplant survival is probably going to be greater, and certainly cheaper. I think it would be important to consider the benefit of imlifidase in highly sensitised patients who fail to get matched via the UK living kidney sharing scheme. Data suggests that the indication for the majority of pairs to enrol in the scheme is due to HLA incompatibility, and not all get matched. Certainly, the likelihood of getting matched if not paired after a few attempts is low. The alternative for these people is to proceed with the HLAi transplant or wait for a deceased donor organ. Due to limited effectiveness of HLAi currently in the UK, most wait for a deceased donor if they cannot find an alternative living donor. A model where these recipients are offered imlifidase, thereby ‘freeing’ up a deceased donor organ for someone without a living donor would provide greater cost effectiveness.</td><td>Comment noted. Thank you for this information. The committee decisions are based upon the indication as outlined in the conditional marketing authorisation. Imlifidase is indicated for ‘adult kidney transplant patients with positive crossmatch against an available deceased donor’. Please see section 2.1 of the FAD for further description.</td></tr>
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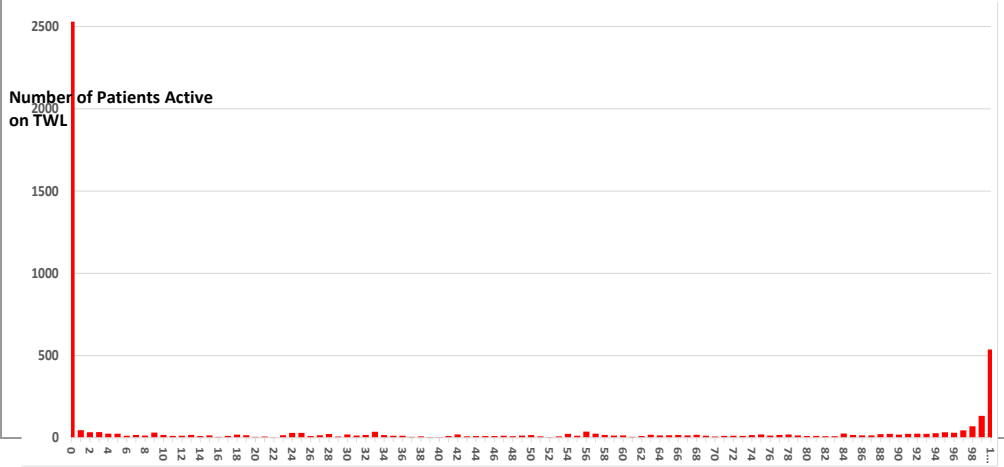
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
22	Consultee	UK Kidney Association	The review highlights the concern of prolongation of cold ischaemic time (CIT) to enable the full evaluation of antibody status post imlifidase. The review group have also raised concern that the CIT maybe so long that there is risk that the organ would be rendered unusable. A lot of centres in the UK, have access to machine perfusion technologies for organ optimisation prior to implantation. If, imlifidase was used in the deceased donor setting, this technology could be adopted to preserve the organ during the cross-match assessment.	Comment noted. The committee further considered the impact of cold ischaemic time at the third Appraisal Committee Meeting. Please see section 3.6 of the FAD.
23	Consultee	UK Kidney Association	The lack of long-term efficacy data negates concern that NICE may not be fulfilling its commitment to 'promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.'	Comment noted. Thank you for noting this.
24	Consultee	British Transplant Society	Thank you for including the British Transplantation Society as a Consultee in the appraisal process for Imlifidase. We have studied the ACD, and have a number of comments. We continue to support the use of Imlifidase in selected highly sensitized kidney transplant candidates, and hope the points below are helpful in reviewing the proposed negative recommendation.	Comment noted. Thank you for providing your feedback.
25	Consultee	British Transplant Society	**Sections 3.1 – 3.4** We are pleased that the committee recognizes both the important advantages of transplantation (life expectancy, quality of life, freedom from dialysis, and important psychosocial benefits) but also the challenges in successfully transplanting highly sensitized patients. Sensitization (immunologic memory against non-self human leucocyte antigens -HLA) is quantified by detecting antibodies against HLA in a serum sample. The calculated reaction frequency (cRF) is the percentage of the last 10,000 deceased against which a transplant candidate has anti-HLA antibodies. A cRF of 0% means there are no significant anti-HLA antibodies (the patient is not sensitized against any HLA), whereas a cRF of 100% means that the patient has anti-HLA antibodies against >99.5% of these 10,000 donors. The distribution of cRF amongst the transplant waiting list (in February 2020, immediately pre-COVID) is shown below:  	Comment noted. Thank you for providing this information.

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			This is important because of 4938 active wait-listed patients half have a cRF of 0%, most of the rest a cRF distributed between 1 and 98%, **but a large minority have a CRF of 99 or 100%** (671 patients – 13.5% of the total active waiting list). The majority of these have a cRF of 100% (537 patients – 10.9% of the active waiting list). Ideally all kidney transplants would be antibody-compatible – that is the recipient has no antibodies against any donor HLA. However for those with a cRF of >99% compatible donors are a rare event – that is why these very highly sensitized patients wait many years for the offer of a kidney (or are never offered a kidney). These patients accumulate on the waiting list leading to the skewed distribution of cRF as shown above.	
26	Consultee	British Transplant Society	**Section 3.5 - Current pathway for cRF >99% patients.** The ERG and committee have reviewed the current approach to the extreme inequity in access to transplantation for these patients, which is referred to throughout the ACD. This approach was introduced in September 2019 following a substantial revision of the National Kidney Offering Scheme operated by NHSBT: • cRF 100% patients are allocated to Tier A of the allocation algorithm. • Donated kidneys are first matched to Tier A, and allocated if antibody compatible to any Tier A patient (prior to 2019 this prioritized allocation was only given to patients who had already been on the waiting list for 7 years) • In the first year of the 2019 allocation scheme 63 kidneys were transplanted into Tier A patients – about 10% of the total, although of course new patients are being added to Tier A all the time. • So even with this new allocation algorithm the median waiting time for a Tier A patient is likely to be >5 years (compared to the median national waiting time of 536 days – substantially less than 2 years). Accordingly these very highly sensitized patients remain profoundly disadvantaged. Moreover, both patients from ethnic minorities and women are over represented in Tier A – the former because of an excess of blood group B patients, and the latter because of HLA sensitization caused by pregnancy (discussed in Section 3.18 of the ACD) Access to transplantation for these patients may be increased by allowing antibody-incompatible transplants. Many transplant centres already allow 'low risk' AIT – those where the recipient has antibodies against donor HLA but at a relatively low level. In general the donor specific antibodies (DSA) are of insufficient titre to cause a positive cellular cross match (that is a cross match performed by flow cytometry (FC) or by complement dependent cytotoxicity (CDC)). However, most of the cRF>99% patients have multiple high level antibodies that would cause a positive cross match against an incompatible donor. Performing a transplant against a positive cross match carries a high risk of early, severe antibody-mediated rejection and graft loss. A positive cross match can be overcome by treatments to remove antibody from the blood (for example plasma exchange), but multiple treatments over several days are needed. Many centres have used antibody-removal protocols to allow planned antibody-incompatible living donor transplants, but these protocols are not possible to allow an incompatible deceased donor transplant because of the short time between the offer of a kidney and the transplant (hours).	Comment noted. Thank you for highlighting these issues. The committee further discussed the access to transplantation for people who are highly sensitised further at the third Appraisal Committee Meeting. Please see sections 3.2; 3.8; 3.9 and 3.16 of the FAD.

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			Imlifidase offers, for the first time, the opportunity of an antibody incompatible deceased donor kidney transplant. The manufacturer of Imlifidase has provided data from several uncontrolled studies demonstrating that Imlifidase is able to remove DSA from the circulation (and thus convert a positive cross match to a negative cross match) in the majority of treated patients (52 out of 54 treated patients – 96.3%). Despite a significant incidence of antibody-mediated rejection (as DSA are resynthesized weeks – months after Imlifidase treatment), medium-term outcomes are good despite the necessarily limited data and uncontrolled nature of the trials.	

27	Consultee	British Transplant Society	The ACD raises a number of specific points which we have addressed directly:
			
			Section 3.6 – The proposed treatment pathway likely underestimates the impact of cold ischaemic time of the donor kidney
			There are a number of inaccurate assumptions in this section:
			• *Before an Imlifidase infusion can be started a cross match test is needed*. This is partly correct, but the cRF>99% patients on the waiting list considered eligible for Imlifidase have an extensive history of HLA antibody screening. Thus, when a kidney is offered the cross-match result can be determined at once, using contemporary HLA antibody screening results – a 'virtual cross match'. Importantly, kidneys are usually offered before the retrieval operation has taken place. Accordingly, the patient can be admitted to the transplant unit and the virtual cross match reported *before* any cold ischaemic time has been accrued.
			• As soon as the kidney is retrieved, and the retrieving surgeon has confirmed that it is transplantable, the Imlifidase infusion can be started
			• Six hours after the infusion a further HLA antibody screen is needed to conform that the DSA have been eliminated from the circulation – a test that takes about 4 hours.
			• So from retrieval to reporting of the post-Imlifidase HLA antibody screen would result in a very reasonable cold ischaemic time of <12 hours. During this time the kidney would be in transit from the donor hospital, and the patient readied for the transplant operation – for example receiving dialysis. These processes take place concurrently, not sequentially.
			
			• *The committee considered that the variation in timings could mean there is a risk that the kidney is wasted.* We consider this outcome to be so unlikely that it should not be part of the ACD. As outlined above, the process of administering Imlifidase and performing a post-treatment cross match is not associated with excessive cold ischaemia. There is good evidence from the UK that, for DBD kidneys, a cold ischaemic time of up to 24 hours is not associated with adverse outcomes[1]. Even if the Imlifidase treatment is not successful, and the kidney needs to be re-allocated, then there are robust systems already in place to do so in a timely fashion – the 'Fast Track' system.
			• In fact it is common for kidneys to be transported to a transplant centre that, often many hours after retrieval, determines that the kidney cannot be transplanted:
			
			  ○ Kidneys offered as part of a kidney + pancreas transplant, but with the pancreas deemed unsuitable for transplantation.
			  ○ An unexpected positive cross match
				Comment noted. Thank you for providing this detail. The committee considered this as well as information provided by other consultees. It further discussed the impact of cold ischaemic time at the third Appraisal Committee Meeting. Please see section 3.6 of the FAD for the committee considerations.

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			○ Medical complications in the recipient • We believe that concerns over cold ischaemic time and the theoretical risk of a kidney being wasted are unfounded.	
28	Consultee	British Transplant Society	**Section 3.7 – Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are non-sensitized.** We do not believe this concern is justified. Quite clearly a donated kidney can only be transplanted into one patient, and so the other 5000 or so patients on the waiting list necessarily do not receive that kidney. This is the case every time a kidney is allocated – whether to a sensitized or non-sensitized patient. All patients are listed on a single national waiting list, and under the current pathway sensitized patients are profoundly disadvantaged. The use of Imlifidase seeks to correct this inequity. The argument that a non-sensitized patient may somehow be disadvantaged makes no sense at all. Particularly important is the consensus view that those cRF>99% patients considered for Imlifidase should have been wait-listed for a period of time (at least 2 years) before becoming eligible for Imlifidase. This approach: • Allows for a reasonable opportunity that a compatible kidney is allocated to cRF>99% patients • Means that cRF>99% patients will already have accrued waiting time greater than the national median and thus likely ranked above non-sensitized patients in the allocation algorithm whether or not Imlifidase is used. The committee is also concerned that 'the clinical (and cost) effectiveness would be lower for some transplants using Imlifidase'. It may well be true that graft survival following a high risk incompatible transplant facilitated by Imlifidase is likely less good than if the same kidney were used as a compatible transplant. But this is a poor argument. There are many other patient characteristics that predict less good outcomes – for example the recipient's age, or presence of diabetes – but we do not discriminate against those patients by offering kidneys only to young fit recipients likely to have the best outcomes. We believe that it is unfair to discriminate against cRF >99% patients on the grounds of inferior outcome – particularly when the only alternative is a life on dialysis.	Comment noted. Thank you for providing these details. The committee considered this information as well as information provided by other consultees at the 3rd Appraisal Committee Meeting. Its discussions are reported in section 3.8 of the FAD.
29	Consultee	British Transplant Society	**Section 3.8 – The available outcome data is currently too short term to decide whether Imlifidase can be used in the NHS.** **Section 3.9 – Some antibody-mediated rejection is expected but people who are highly sensitized may have better outcomes if they wait for a match in the new algorithm** **Section 3.11 – Data shows that some people for whom Imlifidase might be suitable already have access to transplants** It is correct that long-term data on outcomes is limited, but given the highly specialized nature of antibody-incompatible transplants this is almost inevitable. Never the less the 3-year outcomes reported by Kjellman in Imlifidase-treated patients[2] are at least as good as those in antibody incompatible live donor transplants in the UK[3,4]. In all of these reports antibody-mediated rejection is inevitable – close to 40% in the highest risk recipients (those with sufficient DSA to give rise to a positive CDC cross match). We agree with the ACD that cRF>99% patients should have been on the deceased donor waiting list for sufficient time to be allocated a compatible kidney if such an offer is realistic. The quoted	Comment noted. Thank you for providing this detail. The committee considered all the evidence submitted, as well as considering additional stakeholder comments. It discussed this issue further at the third Appraisal Committee Meeting and has revised its conclusions. These discussions are reported in section 3.9 of the FAD.

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			figure of 31.4 % of these patients receiving a compatible kidney seems reasonable – likely realized within 3-4 years waiting in Tier A (see comments on Section 3.5 above). But this still leaves the majority of cRF>99% patients without a transplant. Certainly the introduction of Imlifidase in the UK should be a careful and nationally coordinated process, including: • Mandated waiting time in Tier A to allow the opportunity of a compatible transplant • Careful selection of acceptable but incompatible HLA specificities aiming to avoid transplants with strong positive CDC cross match, thus reducing the incidence of AMR and improving long-term outcomes[3,4]. • Avoiding patients with extreme levels of DSA thus reducing (even eliminating) the risk of a patient receiving Imlifidase but not achieving clearance of DSA and thus not proceeding to transplant. We believe that the robust, centralized, and national transplant system operated by NHSBT lends itself perfectly to the careful introduction of Imlifidase in the UK, and to the collection of data that will quickly inform the most appropriate use of Imlifidase in this very challenging group of patients.	
30	Consultee	British Transplant Society	**Section 3.12 – Not everyone who has Imlifidase treatment goes on to have a kidney transplant, but the exact proportion is uncertain.** This does not seem a reasonable concern. 52 out of 54 Imlifidase-treated patients in the series reported by the company did receive a transplant – 96.3%. Careful patient selection (see above) may further reduce the risk of a non-proceeding transplant.	Comment noted. Thank you for highlighting this.
31	Consultee	British Transplant Society	**Section 3.14 – The number of cross match tests will likely be higher than 1 and should be included in the economic model.** The robust detail of HLA antibody screening for wait-listed patients in the UK is described in the comments on Section 3.6. This applies to all wait-listed patients – cRF>99% or not. A post-Imlifidase test (cellular or virtual cross match) is absolutely required, but for the majority of patients this would be just one cross match. Careful patient selection (see above) would negate the need for a second Imlifidase infusion (in any case a rare event – only 3 of the patients in the various series reported). In any case, the cost of a cross match is negligible compared to that of transplantation in general and Imlifidase in particular.	Comment noted. This section documented in the ACD has now been removed from the FAD.
32	Consultee	British Transplant Society	**Section 3.19 – Imlifidase could provide a step-change in treatment but there are challenges in implementation.** In many ways this is the central issue. We hope that, in the points above, we have outlined how Imlifidase can be effectively introduced in the UK taking advantage of our coordinated national transplant program. We believe we have addressed the practical concerns raised in the ACD and encourage the committee to revise their recommendation.	Comment noted. Thank you for raising these issues. Please see section 3.17 of the FAD.
33	Consultee	British Transplant Society	**References** 1. Summers *et al* (2015). Kidney donation after circulatory death (DCD): state of the art. *Kidney Int* 88, 241-249 2. Kjellman *et al* (2021). Outcomes at 3 years post-transplant in Imlifidase-desensitized kidney	Thank you for providing these references.

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			transplant patients. *Am J Transplant* 21, 3907-3918 3. Higgins *et al* (2011). Human leucocyte antigen antibody-incompatible renal transplantation: excellent medium-term outcomes with negative cytotoxic crossmatch. *Transplantation* 92, 900-906 4. Pankhurst et al (2017). The UK national registry of ABO and HLA antibody-incompatible renal transplantation: pre-transplant factors associated with outcome in 879 transplants. *Transplant Direct* 3, e181	
34	Consultee	NHS England & NHS Improvement	We were pleased to see that the ACD recognised the very positive potential benefits of Imlifidase including: • *"Renal replacement therapies while waiting for a kidney transplant can have a substantial effect on quality of life"* (page 5) • *"People who are highly sensitised wait longer for a suitable donor kidney than those who are not sensitised"* (page 6) • *"People who have waited a long time for a transplant may not be well enough to have one by the time a suitable donor is found"* (page 7) • *"Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people"* (page 7) • *"The proposed population might be appropriate but needs to be considered in the context of current NHS clinical practice"* (page 8) • *"But, despite this [introduction of the new UK organ offering algorithm] there are still people who would be able to have a transplant if Imlifidase were to become available" (page 9)* We would like to comment on the reasons that the ACD concludes that the therapy cannot be recommended:	Comment noted. Thank you for providing your feedback.
35	Consultee	NHS England & NHS Improvement	**Initial Comments.** Regarding the first point above, it should be recognised that a kidney transplant not only transforms patients' quality of life but **also** a significant improvement in life expectancy compared with long-term dialysis (and this is greater, the younger the patient is). We disagree with the company's suggestion that patients should be offered this therapy after waiting for at least two years. As the ACD points out, the latest NHSBT kidney offering scheme introduced in 2019 was modelled and designed to improve access to HSP. However, this scheme has not had an opportunity to demonstrate if this modelling correctly predicted the improved access to deceased donor kidneys for highly sensitised patients (partly because it has only been in use for just over 2 years but confounded by the Covid pandemic). In our opinion the therapy should be reserved for patients waiting at least four or five years to give time for a potential antibody compatible deceased donor kidney to be offered. However, after four or five years there is a significant increase in cardiovascular morbidity and mortality in patients remaining on dialysis. Initially, only patients falling into Tier A should be offered the treatment.	Comment noted. Thank you for providing this information. Following the third Appraisal Committee Meeting, the committee has revised its recommendations. These are reported in section 3.1 of the FAD.
36	Consultee	NHS England	***Specific Comments.***	Comment noted. Thank you for providing

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		& NHS Improvement	*Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised: (page 12)* and *"Stakeholders explained that any donor kidney used with imlifidase could have been used for someone else with much lower costs, better outcomes and equal related savings from avoiding dialysis"* This is true and important but the HSPs are currently severely disadvantaged. Of course, whenever any patient receives a deceased donor kidney, another patient does not.…all patients (incl HSP) on the active W/L are in a pool…if one patient receives a kidney someone else doesn't…imlifidase recipients aren't ***additional*** to the other patients on the W/L…so we don't understand this argument, especially since the HSPs are already disadvantaged.	this information. The committee considered these points in its discussions at the third appraisal committee meeting. These have been reported in section 3.8 of the FAD.
37	Consultee	NHS England & NHS Improvement	*The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS* The outcome data is necessarily short although the three-year data published by Kjellman et al (2021) does demonstrate comparable outcomes to other highly sensitised patients undergoing HLA incompatible transplantation. We appreciate that the inclusion criteria in this published cohort does not include only patients who would fit the proposed use of Imlifidase in the NHS, but we do not believe that a randomised controlled trial is possible. There are considerable data in the literature indicating the benefit of "desensitising" highly sensitised patients compared with those left to wait for an antibody compatible kidney transport, or never being offered one (see 10 below). We agree that more data are required, and would be acquired if the therapy were adopted. The ERG and the Committee have identified important concerns such as the numbers of patients not proceeding to transplantation after treatment, the potential wasting of a donor kidney, which we think is likely to be very small indeed.	Comment noted. Thank you. The committee considered all the evidence submitted, as well as considering additional stakeholder comments. It discussed this issue further at the third Appraisal Committee Meeting and has revised its conclusions. These discussions are reported in section 3.9 of the FAD.
38	Consultee	NHS England & NHS Improvement	*The proposed treatment pathway likely underestimates the impact on cold ischaemic time of the donor kidney* The ACD states "A time of more than 24 hours would mean the donated kidney effectively becomes unusable for transplant." (page 10). This is untrue for DBD Kidneys (Summers et al 2013[1], which analysed UK NHSBT data). In most cases, the potential highly sensitive patient would be brought to the hospital as soon as the potential donor have been identified. There will be no need to perform a cross match before Imlifidase administration because this would be predicted from the laboratory knowledge of the patient's antibody profile and donor HLA. We envisage that treatment would be given as soon as the donor kidney is retrieved and, in the opinion of the retrieving surgeon, to be suitable for implantation. By the time the kidney arrives at the transplant centre usually, within 8-10 hours, a cross match could be performed and if negative transplantation could follow as soon as theatre is available. Even if a second treatment were necessary in most cases transplantation could proceed at or shortly after 24 hours. In the unlikely event of a repeat positive cross match the kidney could be transplanted into another antibody compatible recipient, who could be brought in as a backup to prevent a further delay in transplantation and increased cold ischemic time. Reference Summers, D.M., et al., *Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study.* Lancet, 2013. **381**(9868): p. 727-34	Comment noted. Thank you for providing this detail. The committee considered this as well as information provided by other consultees. It further discussed the impact of cold ischaemic time at the third Appraisal Committee Meeting. Please see section 3.6 of the FAD for the committee considerations.

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39	Consultee	NHS England & NHS Improvement	*Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm* This is true, but patients in the target population (already waiting > 7 yr and highly sensitised or matchability 10 and cRF >99%) are very unlikely to receive an antibody compatible kidney. Although patients with ABMR are likely to have a reduced transplant survival, this can still be many years, reducing cardiovascular morbidity and greatly improving quality of life whilst the transplant is working. Furthermore, although 40% of patients did have ABMR, 60% did not. In the 3 year follow up study of 39 Imlifidase treated patients with positive cross-match, the graft survival was similar- actually 93% ABMR+ and 77% ABMR-, although the patients who suffered ABMR had less good function (eGFR 48.5 ml/min v. 60.5 ml/min).	Comment noted. Thank you for providing this information. The committee considered this issue further at the third Appraisal Committee Meeting. Its discussions are reported in section 3.10 of the FAD.
40	Consultee	NHS England & NHS Improvement	*Data shows that some people for whom imlifidase might be suitable already have access to transplants* Clearly this is true, but again surely the issue pivots on how long a highly sensitised patient is likely to wait for an antibody compatible kidney and whatever the company's lower estimate is (redacted), even if the 31.44% stands, the vast majority of patients will not get a transplant and, as pointed out above, every year on dialysis adds to the cardiovascular morbidity and mortality.	Comment noted. Thank you for highlighting. This section documented in the ACD has since been removed from the FAD.
41	Consultee	NHS England & NHS Improvement	*Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain* We believe that it is agreed that the vast majority, more than 96% of eligible patients receiving imlifidase ***will*** be transplanted, which seems a small number to exclude its use for the majority.	Comment noted. Thank you for highlighting this.
42	Consultee	NHS England & NHS Improvement	*The number of crossmatch tests will likely be higher than 1 and should be included in the economic model* "…To account for this the ERG applied the costs of 2.4 crossmatch tests in its preferred base case" Firstly, this seems excessive. Our understanding is that only 3/46 recipients required a second dose of imlifidase, although 1 received a second dose based on a 2 hr post imlifidase sample although the 6 hr sample was actually negative, so 2/46, <5%. In any case most units would do a crossmatch post-transplant even when the pre-transplant cross match was virtual, so no extra crossmatch and the cost of the crossmatch is tiny in relation to the other costs.	Comment noted. This section documented in the ACD has since been removed from the FAD.
43	Consultee	NHS England & NHS Improvement	*The committee was aware that while there may be better quality of life initially after transplant, overall quality of life for some people after imlifidase and a transplant may be lower compared with the overall population who have a transplant without imlifidase.* We agree that this MAY be the case, but the correct comparator for the successfully transplanted imlifidase recipient is with patients on long-term dialysis who either never get a transplant or have to wait many years, both of which are associated with much poorer quality of life and shorter life expectancy	Comment noted. This section documented in the ACD has also been removed from the FAD.
44	Consultee	NHS England & NHS Improvement	*"Evidence for the clinical effectiveness of imlifidase originally came from 4 non-UK based, uncontrolled, open-label studies. The primary outcomes reported on safety and ability to achieve a crossmatch conversion after treatment with imlifidase. For this reason, they had short follow-up times that ranged between 64 days and 180 days."* Because the number of patients eligible for imlifidase treatment is small and since "control" patients may wait very many years or never receive a transplant without imlifidase, a controlled trail is not	Comment noted. Thank you for noting this. The committee discussed this issue further at the third Appraisal Committee Meeting. Please see section 3.9 of the FAD.

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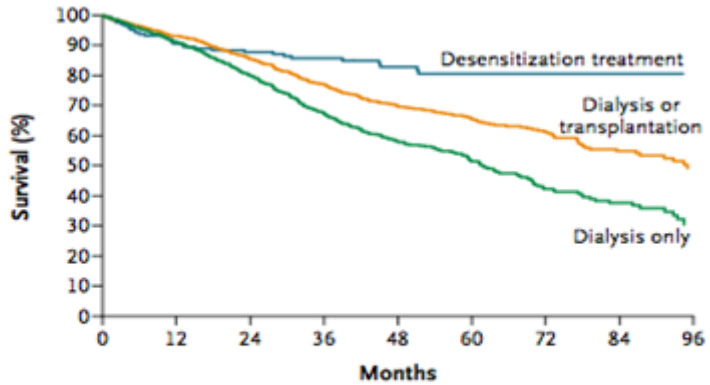
			practical. As the Committee & ERG are aware there are now 3-yr outcome data, and the KM plots are flat by 3 yr and this is similar to data on desensitised patients.	
45	Consultee	NHS England & NHS Improvement	1. *"Clinical opinion sought by the ERG suggested that longer-term data beyond 3 years would be needed to better determine clinical outcomes, especially on graft survival and health-related quality of life, for people who have a transplant with imlifidase. The company has planned a phase 3, controlled, non-randomised, open-label study. The committee considered that long-term outcomes reported in this would be critical but that there was currently not enough data available from this study to inform decision making."* We agree that longer term graft and patient survival are ideally needed but believe that there are data that are applicable in this setting. For example, Montgomery et al who reported on more than 2300 HSP suitable for transplantation. 210 had desensitisation while 1027 remained on dialysis but received a transplant at some stage and 1012 patients were not transplanted by the time of analysis (see figure below). Clearly desensitisation (with prior positive crossmatch) demonstrated superior survival (even if the transplant failed) and the Committee and ERG accept that life with a transplant provides a much-improved quality of life.  **No. at Risk** Desensitization treatment 210 170 143 110 75 58 42 28 14 Dual therapy 1027 854 688 497 321 230 157 96 41 Dialysis only 1012 822 626 419 250 159 93 54 17 Patient survival after transplantation following desensitisation Montgomery, R.A., et al., *Desensitization in HLA-incompatible kidney recipients and survival.* N Engl J Med, 2011. **365**(4): p. 318-26.	Comment noted. Thank you for providing this reference. The committee further considered the clinical evidence at the third Appraisal Committee Meeting. It concluded although there was a lack of medium or long-term outcome data, this provided the best currently available data.(Please see section 3.9 of the FAD).

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46	Consultee	NHS England & NHS Improvement	We note in the ACD acknowledges that "Imlifidase could provide a step-change in treatment but there are challenges in implementation." (Section 3.19). We believe this is truly a step change innovation that would, if introduced into the NHS, allow a relatively small number of highly disadvantaged patients receive a kidney transplant that they would otherwise be very unlikely to access, improving both quality and quantity of life. We hope that the NICE committee consider our comments countering reasons why the ACD has, prior to consultation, not recommended its introduction by the NHS and urge revision of the provisional decision.	Comment noted. Thank you for your raising these points. The committee considered this information as well as information provided by other consultees. It further discussed the impact of cold ischaemic time at the third Appraisal Committee Meeting. It has revised its recommendations. These are reported in section 3.1 of the FAD.
47	Web comment	NHS blood and transplant	**Has all of the relevant evidence been taken into account?** No. Comprehensive evidence about rejection rates and outcomes for antibody incompatible transplantation is lacking.	Comment noted. Thank you for highlighting.
48	Web comment	NHS blood and transplant	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I feel the interpretations of clinical effectiveness are not always consistent with all the available evidence.	Comment noted. Thank you for highlighting.
49	Web comment	NHS blood and transplant	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No, not yet.	Comment noted. Thank you.
50	Web comment	NHS blood and transplant	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** This form of treatment is essentially about equity of access to transplantation where age, gender and race can be associated with being disadvantaged.	Comment noted. Thank you for highlighting.
51	Web comment	NHS blood and transplant	**General comments** Section 1: The Title of the appraisal consultation document is misleading. The implication is that Imlifidase prevents rejection. Misleading because there are many types of rejection. Imlifidase use is to prevent hyperacute rejection caused be pre-existing donor-specific antibodies. Other types of rejection, such as acute and chronic AMR and ACR should be unaffected by Imlifidase.	Comment noted. We have now amended the title. This now reads "Imlifidase for desensitisation treatment for preventing kidney transplant rejection in people with chronic kidney disease"
52	Web comment	NHS blood and transplant	**1.2: Using imlifidase might substantially increase the time from a kidney being donated to the transplant taking place.** "might substantially increase cold ischaemia time (CIT)" – a process should be designed to avoid this (Peacock et al 2022, IJI). The UK has recently developed crossmatching guidelines designed to minimise CIT. A key principle is to complete testing before the donor organ arrives at the transplant centre. This can be accomplished by using pre-donation blood samples from the donor	Comment noted. Thank you for providing this reference. The committee considered this as well as information provided by other consultees. It further discussed the impact of cold ischaemic time at the third Appraisal Committee Meeting. Please see

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			and virtual crossmatches (VXM). This framework could be used in the context of pretransplant antibody reduction by Imlifidase treatment. The VXM uses existing antibody data, both level and specificity, and an experienced HLA laboratory should be able to assess potential suitability. Donor offering is an early event in the transplant process and an immediate VXM could be used to assess suitability and necessity for Imlifidase use	section 3.6 of the FAD for the committee considerations.
53	Web comment	NHS blood and transplant	**3.2: although a small number of people could wait up to 7 years.** It is stated the "a small number of people could wait up to 7 years". This is misleading. Such people are likely to wait more than 7 years and as such this group accumulates on the waiting list. On the W Midlands waiting list (about 10% of UK), for example, there are 36 people who have been waiting for more than 7 years (median of 10.4 years), 33 of whom have a CRF of 100%.	Comment noted. Thank you for clarifying. This has been updated in the FAD and now reads "although a small number of people could wait more than 7 years". Please see section 3.2 of the FAD.
54	Web comment	NHS blood and transplant	**3.4: Because the treatment has a transient effect, antibody levels in the body rise after transplant.** The transient effect of Imlifidase is very similar to that of plasmapheresis used in this context: both are designed to reduce pre-transplant HLA antibodies. Desensitisation by various forms of plasmapheresis has been used in the UK since about 1984. The early rise after the transplant is seen with both forms of treatment. This has been well documented by the Coventry group (plasmapheresis used) and is usually associated with good outcome as in most cases the antibodies fall spontaneously (Higgins et al 2009. Transplantation).	Comment noted. Thank you for highlighting this.
55	Web comment	NHS blood and transplant	**3.5: a CRF of 100%** A CRF of 100% actually covers a range of sensitisations. The CRF of 100% term used in the UK refers to those cases of 99.5% and over. If the CRF is considered to two decimal places the impact of the 2019 allocation scheme is likely to look very different. This can be seen from the USA experience where new allocation scheme based on the same principles (priorities to long waiters and the highly sensitised) was introduced in 2014 (the US calculates CRF, or PRA, to two decimal places). Improved access to donors was seen in those with a CRF between 99.5% and 99.95%, but not in those with a CRF>99.95% (Stewart et al, AJT 16; 1834-1847. 2016). Many of the UK waiting list patients will have a CRF>99.95%, some are 100.00%. A person with a CRF of 99.95% might expect less than one HLA and ABO compatible donor per year; those with a CRF of 99.99%, about one every ten years; those with 100.00%, none. In contrast, someone with a CRF of 99.5% (also called 100% in the UK) can expect around 5 ABO and HLA compatible donors pa.	Comment noted. Thank you for providing this detail. The committee noted that protocols that would need to be developed by the NHS when using imlifidase would be clinically led, and would consider CRF as well as other factors. Please see section 3.19 of the FAD.
57	Web comment	NHS blood and transplant	**3.7: The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS** The clinical effectiveness of Imlifidase is about its ability to remove HLA antibody reactivity. This is therefore an alternative to plasmapheresis and in this its effectiveness is proven. There is a mortality risk associated with plasmapheresis (eg fatal hypotension) so Imlifidase is likely to be a safer approach to antibody depletion. Post-transplantation events are more likely to depend on the same factors for Imlifidase treatment as with plasmapheresis desensitisation. Longer term outcomes are therefore likely to resemble those seen with plasmapheresis desensitisation and in the UK there are centres with extensive experience. The largest UK single centre outcomes have been published recently (Krishnan et al 2021) which shows overall good outcomes and how to avoid the higher risk cases.	Comment noted. Thank you for providing this information and reference. The committee considered all the evidence submitted, as well as considering additional stakeholder comments. It discussed this issue further at the third Appraisal Committee Meeting and has revised its conclusions. These discussions are reported in section 3.9 of the FAD.
57	Web comment	NHS blood and transplant	**3.9: Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm** This statement is incorrect. An antibody-mediated rejection (AMR) rate of 40% is consistent with	Comment noted. . The committee discussed this issue further at the third Appraisal Committee Meeting. Its

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			HLA antibody incompatible transplantation in general and is seen with plasmapheresis desensitisation. Imlifidase is not and anti-AMR agent. An AMR rate of 10% would be consistent with a standard risk transplant (antibody compatible). Therefore a 40% AMR rate with Imlifidase treatment is expected.	discussions are reported in section 3.10 of the FAD.
58	Web comment	NHS blood and transplant	**3.13: Therefore it could be reasonable to assume that graft survival is worse in people who are highly sensitised,** There is good evidence that graft survival is worse in highly sensitised recipients who receive an incompatible kidney (from conventional antibody removal). The risks, though, are not the same for all people and we now understand who are the higher risk cases and who could be excluded (Krishnan et al, 2021). Those with the strongest antibodies, identified by a cytotoxic crossmatch (CDC), due to higher levels and multiple donor-specific antibodies, have a significantly short graft life. Graft survival in CDC negative cases is similar to that seen for conventional transplants.	Comment noted. Thank you for highlighting this and providing this reference.
59	Web comment	NHS blood and transplant	**3.18: It concluded that although people who have become highly sensitised through pregnancy may have poorer clinical outcomes, it is unknown whether there would be additional benefit from imlifidase and further information is needed.** This conclusion does not properly fit the evidence. The issue of being pregnancy-induced sensitisation does need special consideration. Firstly, the sensitisation rate in females is higher than in males, for this reason, with about double the rate of being highly sensitised for females. Secondly, graft survival for CDC positive HLA incompatible females is particularly poor. Thirdly, although the early rejection rate in female CDC negative HLA incompatible transplants is high, the outcome in these cases is good: those with early rejection (within the first two weeks) have a similar graft survival to the rejection-free cases (Krishnan et al, 2021). The crossmatch status will depend on a donor's HLA type, thus there must be access to donor offers, and therefore a potential recipient of Imlifidase, to be able to make this assessment (this of course applies to all potential antibody incompatible candidates). Access to these donors and Imlifidase treatment is therefore likely to restore equity of access to transplantation to those whose high level of sensitisation involves previous pregnancies.	Comment noted. The committee discussed this issue further at the third Appraisal Committee Meeting and has amended this conclusion. Its discussions are reported in section 3.16 of the FAD.
60	Web comment	NHS blood and transplant	**3.18: Imlifidase could provide a step-change in treatment but there are challenges for implementation** The challenges to implementation are probably well-rehearsed and understood in centres experienced in the clinical management of desensitisation - the issues will the same. This appraisal does not seem to have recognised that Imlifidase can be seen to be an alternative to plasmapheresis and is effective where plasmapheresis is inappropriate. Imlifidase as a form of desensitisation to allow transplantation in highly sensitised people is certainly novel and in that it has proven to be very effective. Pretransplant desensitisation itself is not novel (the world's first cases were performed in the UK in the mid 1980s). However, plasmapheresis is can be less effective than Imlifidase in that very high levels can be refractory to extracorporeal removal, there are certain people for whom plasmapheresis can be a high risk procedure (mortality from hypotension), and it typically requires multiple, successive sessions over many days. Pre-transplant plasmapheresis then is usually not an option with deceased donors. Imlifidase does solve all these three problems.	Comment noted. Thank you for providing this detail. The committee considered these issues in its decision-making. Please see section 3.17 of the FAD.
61	Web comment	NHS blood and	**3.11: The committee accepted this change and concluded that some people for whom imlifidase might be suitable will already have access to transplants. Comment on section:**	Comment noted. Thank you for highlighting. This was included in the

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		transplant	**Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain** An analysis based on a rounded-up CRF calculation (ie anything 99.5% and over) would be unreliable in support of this statement.	ACD, but has since been amended following comments from other consultees. Please see section 3.12 in the FAD for the updated text.
62	Web comment	Belfast Trust HSC (NI)	**Has all of the relevant evidence been taken into account?** Yes	Comment noted.
63	Web comment	Belfast Trust HSC (NI)	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, although no consideration of live donor kidney transplants, where benefits are greater (longer lasting kidney) and costs less (no opportunity cost for alternate recipient, plus no prolonged cold ischaemic time	Comment noted. The committee decisions are based upon the indication as outlined in the conditional marketing authorisation and is for adults who have a positive crossmatch against an available deceased donor. The details are reported in section 2.1 of the FAD
64	Web comment	Belfast Trust HSC (NI)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No - the 2019 amended deceased donor allocation scheme still fails a sub-group of 100% sensitised recipients. These are often young recipients with a prior failed transplant, who become un-transplantable and die after 10-15 years for co-morbid burden. Imlifidase offers this small cohort a chance for a normal life	Comment noted. The recommendations have been updated following the third Appraisal Committee Meeting. Please see section 1.1 of the FAD.
65	Web comment	Belfast Trust HSC (NI)	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No	Comment noted. Thank you.
66	Web comment	Belfast Trust HSC (NI)	**1.2: Why the committee made these recommendations** In the published literature on imlifidase, no kidneys were discarded for prolonged cold ischaemia. In the UK, the smaller geographic size means that kidneys are typically transported 100-400 miles; the published studies were carried out in USA, France and Sweden, where transport distances are 100-3000 miles, giving longer ischaemic times. This concern of ischaemic time does not exist for live donor kidneys, where donor timing can be co-ordinated with negative cross-match (although this is outside market authorisation). The change in deceased donor allocation in 2019 does make access for sensitised recipients a little better, though in Belfast we still have 5-10% of our waitlist as 100% sensitised with current wait-times of 5-11 years. The concerns for pricing certainly seem reasonable.	Comment noted. Thank you for noting these. The section relating to 'Why the Committee made these recommendations' has since been updated following the committee discussions at the third Appraisal Committee Meeting.
67	Web comment	Belfast Trust HSC (NI)	**3.4: Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people** This group of sensitised patients will always need more intensive maintenance drug regimens, and more treatments for antibody-mediated rejection. This is the case currently with protocols using plasmapheresis and IVIg to achieve negative crossmatch.	Comment noted. Thank you for highlighting this.

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68	Web comment	Belfast Trust HSC (NI)	**3.5: The proposed population might be appropriate but needs to be considered in the context of current NHS clinical practice** Using only for 99%-100% sensitised patients seems very sensible	Comment noted. Thank you.
69	Web comment	Belfast Trust HSC (NI)	**3.6: The proposed treatment pathway likely underestimates the impact on cold ischaemic time of the donor kidney** In Belfast we sometimes request a deceased donor blood sample prior to retrieval of organs for sensitised recipients. This allows crossmatch tests (+/- imlifidase) to be given in advance of organ retrieval, allowing reduced ischaemic times. It might be expected for imlifidase to select kidneys from younger deceased after brain death donors - for these kidneys, ischaemic times up to 36 hours are possible - though admittedly shorter ischaemic time is always better	Comment noted. Thank you for providing this detail. The committee considered this as well as information provided by other consultees. It further discussed the impact of cold ischaemic time at the third Appraisal Committee Meeting. Please see section 3.6 of the FAD for the committee considerations.
70	Web comment	Belfast Trust HSC (NI)	**3.7: Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised** The use of every deceased donor kidney involves an opportunity cost of alternate recipients not transplanted. We already take on lower cost-effective recipients; our diabetic recipients have worse outcomes than average, but we still transplant them. Our sensitised waitlist patients suffer from worst equity of access.	Comment noted. Thank you for highlighting. The committee considerations have been updated following discussions at the third Appraisal Committee Meeting. These are documented in section 3.8 of the FAD.
71	Web comment	Belfast Trust HSC (NI)	**3.8: The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS** The 2021 study of 46 patients provided 3-year follow-up. This timepoint is certainly beyond the area of concern for early graft loss from antibody-mediated rejection. Although not as good as 10-year data, it would be a shame to wait 10 years to provide access to a worthwhile novel treatment.	Comment noted. Thank you for highlighting. The committee considered all the evidence submitted, as well as considering additional stakeholder comments. It discussed this issue further at the third Appraisal Committee Meeting and has revised its conclusions. These discussions are reported in section 3.9 of the FAD.
72	Web comment	Belfast Trust HSC (NI)	**3.9: Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm** 40% antibody mediated rejection is higher than for a standard immunologic risk transplant, but not surprising in this 99-100% sensitised population with incompatible transplants.	Comment noted. Thank you. The committee discussed this issue further at the third Appraisal Committee Meeting. Its discussions are reported in section 3.10 of the FAD.
73	Web comment	Belfast Trust HSC (NI)	**3.16: The most plausible estimates are above what NICE normally considers cost effective and there are substantial issues with implementation** Cost concerns are very reasonable. If younger recipients were recruited, and live donor kidneys which have a longer half-life, then the QALY values would improve If live donor kidneys are used, there is no opportunity cost of a kidney lost to another waitlist recipient - the recipient provides their own unique kidney which would not otherwise have materialised.	Comment noted. Thank you. Considerations about cost effectiveness are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19. The committee decisions are guided by the indication as outlined in the conditional marketing authorisation. This

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				is for adults who have a positive crossmatch against an available deceased donor. Please see section 2.1 of the FAD for details.
74	Web comment	University Hospitals Coventry and Warwickshire	**Has all of the relevant evidence been taken into account?** It is sad to see that a drug which has the potential to be a game changer for highly sensitised patients, who have been waiting on the transplant list for years without a possibility of a live donor, be denied a place for reasons that could be overcome easily. My response to the points raised by the committee are as follows:	Comment noted. Thank you for providing your feedback. The committee has considered feedback at consultation as well as additional information from the company and the ERG. It has now amended its recommendation. Please see the FAD.
75	Web comment	University Hospitals Coventry and Warwickshire	**1, Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease:** Imlifidase is not an anti-rejection drug to prevent antibody mediated rejection (AMR). It is used to create a window, wherein the HLA antibodies against the donor are invalidated, so that an antibody incompatible transplant (AIT) can be performed. Therefore, this drug can be compared to the process of plasmapheresis which is used to remove antibodies over a few days to enable live donor antibody incompatible transplantation.	Comment noted. Thank you for providing this information.
76	Web comment	University Hospitals Coventry and Warwickshire	***2.*** **People who have waited a long time for a transplant may not be well enough to have one by the time a suitable donor is found:** This statement is absolutely true as evidenced by the recent metanalysis which showed that there is significant patient survival benefit with transplantation compared with dialysis (Chaudhry et al, 2022 BMJ). This is why it is important to transplant even highly sensitised individuals so that their survival is increased (Orandi et al, NEJM 2016, Krishnan et al Transplant Direct 2021). Additionally, about 45% of the very highly sensitized (>99.5% calculated reaction frequency [cRF]) wait for over 7 years on the waiting list. Drugs like Imlifidase would be the only option to be able to transplant this cohort.	Comment noted. Thank you for this detail and providing these references. The committee took this into consideration in its decision-making.
77	Web comment	University Hospitals Coventry and Warwickshire	**3. Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people:** This should not come as a surprise as Imlifidase only creates a window where in the HLA antibodies are eliminated (or reduced) to enable a transplant. Imlifidase is equivalent to plasmapheresis for live donor AIT. The chances of rejection needing powerful immunosuppressive medications post AIT is about 40% (Krishnan et al, 2021 Transplant Direct; Stegall et al AJT 2009).	Comment noted. Thank you for your feedback and providing the reference.
78	Web comment	University Hospitals Coventry and Warwickshire	**4. The proposed population might be appropriate but needs to be considered in the context of current nhs clinical practice:** The criteria of cRF >99%, a matchability score of 10 and on the waiting list for more than 2 years seems a reasonable starting point for consideration of Imlifidase in this group of patients. It is possible that the criteria of inclusion could be expanded to other long waiters with cRFs of >95% and could even include live donor transplantation once the success of Imlifidase is demonstrated in this group of individuals.	Comment noted. Thank you. The committee decisions are guided by its indication as outlined in the conditional marketing authorisation. This is for adults who have a positive crossmatch against an available deceased donor. Please see section 2.1 of the FAD for details.
79	Web comment	University Hospitals Coventry and	**5. The proposed treatment pathway likely underestimates the impact on cold ischaemic time (cit) of the donor kidney:** The CIT should start from the time the kidney is removed and not from the time it reaches the	Comment noted. Thank you.

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		Warwickshire	centre. Please refer to my detail response below to question 3, point 2.	
80	Web comment	University Hospitals Coventry and Warwickshire	**6. Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised:** Please refer to my detail response below to question 2.	Comment noted. Thank you.
81	Web comment	University Hospitals Coventry and Warwickshire	**7. The available outcome data is currently too short term to decide whether imlifidase can be used in the nhs:** Please also refer to my detailed response below to question 3 point 1. The use of Imlifidase is for eliminating (or reducing) HLA antibodies, similar to procedures like plasmapheresis. Plasmapheresis unfortunately is not possible in deceased donation due to time constraints which affects the CIT. Moreover, there is an increased risk of bleeding intra-operatively due to the unintended removal of coagulation proteins during the process. In addition, the risk of severe hypotension including the associated risk of morbidity (blindness etc) and mortality, precludes many patients from undergoing plasmapheresis and hence the opportunity to have a transplant. High level of antibodies and certain types of HLA antibodies are not easily removed by plasmapheresis. Thus, an intervention like Imlifidase would be the best option for such patients.	Comment noted. The committee further considered the clinical evidence at the third Appraisal Committee Meeting. It concluded that although there was a lack of medium or long-term outcome data, this provided the best currently available data. Please see section 3.9 of the FAD.
82	Web comment	University Hospitals Coventry and Warwickshire	**8. However, the exact details are confidential and cannot be reported here:** This statement by the committee is rather confusing, as the 3-year outcome paper is available in the public domain. Is there any other data that has been confidentially shared which is of significance	Comment noted. Thank you. This statement was based upon the confidential data the company provided with regarded to its eligible population groups.
83	Web comment	University Hospitals Coventry and Warwickshire	**9. Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm:** Though there is no comparator arm in the company's clinical data, many AIT transplants done post-plasmapheresis in expert centres world-wide have shown an early AMR rate in the range of 40% (Bentall et al, AJT 2013; Marfo et al, CJASN 2011, Locke et al AJT 2007). Therefore, the company's AMR rate of 40% with Imlifidase treatment is expected. Despite the high rate of AMR, the long-term outcomes of AIT are very good (Orandi et al, NEJM 2016; Krishnan et al, 2021 Transplant Direct). With regards to the new kidney offer system (KOS) algorithm, please see my detailed response to question 3, point 3 below.	Comment noted. Thank you for this information and references. The committee considered this issue It discussed this further at the third Appraisal Committee Meeting. Please see section 3.10 of the FAD for these updates.
84	Web comment	University Hospitals Coventry and Warwickshire	**10. A small number of people would not have dialysis before having a transplant with imlifidase:** I agree that it is difficult to estimate the number of such patients. However, this situation is not uncommon especially in individuals whose current transplant is failing but the function is stable enough to not require dialysis.	Comment noted. Thank you for highlighting this.
85	Web comment	University Hospitals Coventry and Warwickshire	**11. Data shows that some people for whom imlifidase might be suitable already have access to transplants:** This statement is not clear. It is like saying that some patients on deceased donor list might already have access to live donors. However, this would not preclude them from being placed on the deceased donor list as the aim is to give these patients a suitable kidney at the appropriate time so that the benefits of transplantation outweigh the risks of waiting on dialysis. Although the new KOS has allowed more transplants in this very highly sensitised group, 90% of the patients in this cohort are still waiting for a transplant. This is the population who should be considered eligible for Imlifidase.	Comment noted. Thank you for this information. This section was originally documented in the ACD but has now been removed from the FAD.

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86	Web comment	University Hospitals Coventry and Warwickshire	**12. Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain:** This is true with any new intervention as patients could have adverse reactions which cannot be predicted.	Comment noted. Thank you.
87	Web comment	University Hospitals Coventry and Warwickshire	**13. Graft survival projections from ibox are highly uncertain so a hazard ratio should be applied to account for this:** These prediction models are not necessarily reliable given the complexity of antibody incompatible transplantation.	Comment noted. Thank you.
88	Web comment	University Hospitals Coventry and Warwickshire	**14. Utility values from li et al. 2017 are an appropriate source for decision making:** It is interesting that the committee has stated that 'after Imlifidase, the overall quality of life may be lower'. This speculation surely should not be a factor in determining whether Imlifidase can be made available for a group of highly sensitised patients. It is important to remember that Imlifidase is like plasmapheresis and therefore the comparators should be the studies on AIT using plasmapheresis. The alternative for not having a transplant with Imlifidase is to wait on dialysis. Many studies have irrevocably shown that the quality of life on dialysis is poor when compared to transplantation. (Jansz et al, Plos One 2016; Rambod et al, Health Care Management 2011)	Comment noted. Thank you for this information. This section was originally documented in the ACD but has now been removed from the FAD.
89	Web comment	University Hospitals Coventry and Warwickshire	**15. Specific consideration needs to be given to people who have become highly sensitised through pregnancy:** Please see my response below to question 4.	Comment noted. Thank you
90	Web comment	University Hospitals Coventry and Warwickshire	**16. Imlifidase could provide a step-change in treatment but there are challenges for implementation:** Yes, Imlifidase is a potential step-change in the treatment of highly sensitised patients waiting for a transplant on the deceased donor waiting list. The challenges of implementation can be sorted by starting with one or two expert centres and expanding later on according to the demand. Please refer to my detailed response below to question 3, point 4.	Comment noted. Thank you.
91	Web comment	University Hospitals Coventry and Warwickshire	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** 1. Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised: This statement almost suggests that it is acceptable to let very highly sensitised die on the waiting list. The cost aspects of the drug should certainly be discussed and negotiated with the company. However, the value of the drug in helping the 8-10% of the individuals on the waiting list get a life line cannot be overlooked. The alternative of staying on dialysis with the associated complications and morbidities, also has a considerable impact on the health economy which cannot be discounted.	Comment noted. The committee considerations have been updated following discussions at the third Appraisal Committee Meeting. These are documented in section 3.8 of the FAD. The committee concluded that kidneys are a scarce resource but decisions should consider opportunity costs as well as equity of access for people who are highly sensitised. (Section 3.8 of the FAD
92	Web comment	University Hospitals Coventry and Warwickshire	**2. The number of crossmatch tests will likely be higher than 1 and should be included in the economic model:** The number of extra CM test when compared to a standard transplant would be 1. Therefore, the total cost of the CMs should be calculated for 2 CMs and not 2.4.	Comment noted. This section documented in the ACD has been removed from the FAD.
93	Web comment	University Hospitals Coventry and	**Are the recommendations sound and a suitable basis for guidance to the NHS?** As mentioned above, the reasons for not recommending this drug are not strong and the issues stated can easily be circumvented.	Comment noted. Thank you for providing your feedback. The committee has revised its decision in light of comments

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		Warwickshire		and analyses received during consultation.
94	Web comment	University Hospitals Coventry and Warwickshire	**1) no long-term evidence to show the benefits of imlifidase:** The use of Imlifidase is for eliminating (or reducing) HLA antibodies, albeit for a brief period, which enables an AIT to happen. Thus, Imlifidase should be compared to procedures like plasma exchange, immunoadsorption, double filtration plasmapheresis etc which are used to reduce the level of HLA antibodies to create a window of opportunity. Therefore, the outcomes of transplant post-Imlifidase is very likely to be similar to those post plasmapheresis. As the centre of expertise with the maximum number of complex AIT transplants post plasmapheresis, our results show that long term graft and patient survival is similar to first-time deceased donor transplantation in the U.K. (Krishnan et al, 2021, Transplant Direct). The overall patient survival of AIT transplantation was 95%, 89%, and 81%; and graft survival was 95%, 85%, and 70% at one, five, and 10 year, respectively, which is similar to the first-time deceased donor transplantation in U.K. Orandi et al, 2016 NEJM, showed that the patient survival of the highly sensitised patients if transplanted was 77% at 8 years post-transplant. The three-year study from the company has also shown similar outcomes of 90% patient survival and 84% graft survival. The UK Renal Registry annual report 2018, showed that 10-year survival of all patients between the age groups of 18 to 64 years, on renal replacement therapy (which includes dialysis and transplants), was 55%. To improve the survival outcome of highly sensitised patients on the transplant waiting list who do not have a live donor, Imlifidase is the only option available currently.	Comment noted. Thank you for providing this information. The committee considered all the evidence submitted, as well as considering additional stakeholder comments. It discussed this issue further at the third Appraisal Committee Meeting and has revised its conclusions.
95	Web comment	University Hospitals Coventry and Warwickshire	**2)imlifidase could increase the risk of donor kidneys becoming unusable:** Yes, CIT could potentially increase beyond 12-18 hours; however, there are easy ways to circumvent this issue and ensure that the donor kidney is not wasted with the use of Imlifidase. i) Imlifidase would potentially be used only in highly sensitised patients who would have had prior delisting of selected antibodies. The quantification of these antibodies can be made available from the most recent blood sample. If this blood sample is less than a month (or even two) old, then one can be certain that the crossmatch (CM) is very likely to remain unchanged. Thus, a virtual CM would be more than sufficient to decide if the patient could be given Imlifidase. A wet CM should also be requested simultaneously to compare the quantification with a wet CM that would need doing 6 hours post infusion. This would ensure the CIT is not unduly increased. ii) The company has suggested that a few patients may need a second dose of Imlifidase if the CM is not converted to negative after the first dose. The second dose could potentially make the CIT much longer as another CM needs to be done after 4-6 hours after the first dose of Imlifidase. As the process of CM takes about 4 hours, an additional dose could add an extra 8-10 hours as the same process has to be repeated again. Looking at the company's previous publications, it seems that less than 5% of the patients had required a second dose. As one dose is sufficient to convert to a negative CM for 95% of the highly sensitised patients, the protocol should be changed to only one dose as a norm. However, if need be, a clause can be added to include a second dose in case of a persistent positive cross match IF the benefits of the second dose far outweighs the risks of increasing CIT and potential DGF. iii) It is not an uncommon practice to get a potential recipient as a backup during deceased donation	Comment noted. Thank you for providing this detail. The committee considered this as well as information provided by other consultees. It further discussed the impact of cold ischaemic time at the third Appraisal Committee Meeting. Please see section 3.6 of the FAD for the committee considerations.

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			in some units. This practice can be made mandatory if a patient is being considered for Imlifidase. The backup recipient can be transplanted if: a) the first patient has an adverse reaction to the drug b) after the first dose the cross match remains positive. However, experienced centres in AIT may proceed to transplant the first patient at a low level of antibodies i.e- Cytotoxic negative but flow positive or cytotoxic negative, flow negative but luminex positive c) on very rare occasions after the second dose if the CM does not become negative iv) As use of machine perfusion is increasing currently, one could possibly consider machine perfusion for kidneys intended for highly sensitised patients eligible for Imlifidase. Kruszyna et al Transplant Proceedings 2021, showed that hypothermic machine perfusion significantly reduced delayed graft function and compensated for extended storage time.	
96	Web comment	University Hospitals Coventry and Warwickshire	**3) changes to the uk kidney offering scheme (kos)2019 have improved access for people who are highly sensitized and hence they may have improved access without imlifidase:** According to the data from NHSBT, there has been an increase of 10% transplantation in these highly sensitised patients after the change in the KOS. It is well known that patients who are very highly sensitized i,e >99.5% cRF comprise about 10% of the waiting list. Even if the new KOS has increased the transplantation rate by 10% which equates to 1% of the very highly sensitised cohort, what happens to the remaining 9% (i,e 90% of this group)? Stewart et al AJT, 2016 showed that the rate of transplant in the group who have greater than >99.95% cRF is significantly less than those with lower cRF, despite the changes in their allocation policy. They also showed that there is a bolus effect where by the rate increased initially but reduced later. Moreover, the highly sensitized group will be increasing constantly due to the use of expanded donor criteria and fast track organs. As Metzger et al pointed out in AJT 2003, the use of these organs would result in increasing sensitization as these grafts do not last as long as standard deceased donor grafts. Every new patient joining in Tier A in the new KOS, would further disadvantage the existing highly sensitised group. Thus, though the KOS has improved the chances of a transplant in this highly sensitised group, the need for a drug like Imlifidase still remains very high to achieve reasonable equity in this group of patients.	Comment noted. The committee further discussed issues of equity at the third Appraisal Committee Meeting. Its discussions are reported in section 3.5; 3.8 and 3.16 of the FAD.
97	Web comment	University Hospitals Coventry and Warwickshire	**4) uncertainty about how imlifidase would be integrated into the existing transplant process:** AIT is a very highly specialized field requiring a lot of expertise and intricate understanding. In addition, the success of the programme depends on the ability of the tissue typing laboratory and the renal transplant unit to function seamlessly as one unit. The use of Imlifidase requires even more coordination. Therefore, if one or maximum two centres with AIT expertise are made as national centres for Imlifidase, the process of integrating the use of Imlifidase into the existing transplant process would become much easier and would also yield the best possible outcomes. This process of learning can subsequently be adapted to include other centres, if need be according to the demand.	Comment noted. Thank you for providing this information and references. The committee carefully considered these issues along with feedback from other consultees in its decision-making at the third Appraisal Committee Meeting.
98	Web comment	University Hospitals Coventry and	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment,**	Comment noted. Thank you for highlighting this. The committee considered this as well as information

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		Warwickshire	**pregnancy and maternity?** As mentioned in my response to question 2, the recommendation regarding the drug unduly disadvantages the 8-10% of the highly sensitized population on the waiting list who do not have a potential live donor to be entered on to the paired exchange. Drugs like Imlifidase are their only chance of getting a kidney transplant currently.	provided by other consultees at the third Appraisal Committee Meeting.
99	Web comment	University Hospitals Coventry and Warwickshire	**Specific consideration needs to be given to people who have become highly sensitised through pregnancy:** Pregnancy increases the chances of patients becoming very highly sensitised and hence these patients would benefit from Imlifidase. However, all patients who are very highly sensitised should be considered equally eligible for Imlifidase.	Comment noted. The committee further discussed these issues at the third Appraisal Committee Meeting. Its discussions are reported in section 3.16 of the FAD.
100	Web comment	North Bristol NHS trust	**Has all of the relevant evidence been taken into account?** The 2019 KoS on simulation modelling is expected to increase the number of Highly sensitised patients (HSP) from 2% to 4% per year. The simulation modelling clearly showed that this improvement will plateau at approximately 4% and there will not any further year-on-year increase. Biologically (due to the limited HLA types in the organ donor pool) and statistically (as evidenced by simulation modelling prior to 2019 KoS introduction) it is implausible that the KoS will significantly decrease or eliminate the problem of long waiters due to HLA sensitisation. Without access to the pre-implementation KoS simulation modelling, the panel may have mistakenly concluded that the new KoS would reduce the need for additional intervention/s to improve outcomes for HSP. With approximately 20% (>1000 patients) of national kidney transplant waiting list consisting of HSP - it is clear that multiple interventions including the revised KoS and agents such as Imlifidase will be key to improve outcomes. These interventions will benefit different patient groups within the HSP population and as such are not mutually compete for the same patient sub-groups.	Comment noted. Thank you for providing this information. The committee considered these points as well as issues raised by other stakeholders in its decision-making.
101	Web comment	North Bristol NHS trust	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The assumption that kidneys not used for HSP (following treatment with Imlifidase) could benefit other recipients on the waiting-list with better cost-effectiveness needs re-evaluation. Please consider reviewing the manuscript by Bernadette Li et al Equity–Efficiency Trade-offs Associated With Alternative Approaches to Deceased Donor Kidney Allocation: A Patient-level Simulation, Transplantation, Apr 2020, Vol 104, 795-803. This clearly establishes a completely Utility skewed allocation model does not provide overall best ICER/cost per QALY return. Unlike other treatments NICE may consider, the cost to the tax payer is comparing costs of on-going dialysis vs cost of Imlifidase enabled transplantation. A non-transplanted patient continues to accrue costs related to dialysis whilst having declining health status as dialysis is inferior to transplantation. Therefore, comparisons has to be between treatment enabled transplantation vs continued dialysis and not against a control group of transplanting an un-sensitised patient who does not require any additional intervention.	Comment noted. Thank you for providing this detail and the reference.
102	Web comment	North Bristol NHS trust	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The risks associated with prolonged cold ischaemia time (CIT) are over stated and do not take into account likely clinical practise in a small number of expert centres that can implement an Imlifidase enabled pathway. For eg: it is likely the clinical model could be that these specialised centres would only accept offers from high quality (D1 or D2 in the donor risk quartiles) organ offers for patients who require Imlifidase. These organs are more likely to be able to tolerate the prolongation of CIT from an average of 12 hrs to 18 hrs due to the additional time required for post-Imlifidase cross	Comment noted. Thank you for highlighting these issues. The committee has since revised its recommendations following the third Appraisal Committee Meeting. The committee further discussed the impact of cold ischaemic time at the third Appraisal Committee Meeting.

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			match. Peripheral blood cross match soon after organ offer acceptance will further help to reduce any CIT accumulating even before organ retrieval is complete. Therefore, within expertly designed pathways for this niche group - kidney transplantation can be done within easily acceptable CIT thresholds of <20 hours and organs accepted will be of sufficient quality to not suffer significant harm by the CIT increase of ~6 hours. The only other alternative for this patient population is to wait for a long time on the national deceased donor list - denying these patients the opportunity to transplantation because of CIT prolongation of ~6hrs or because 'it is too hard' to incorporate Imlifidase in the patient pathway is disproportionate as the alternative risks of no transplantation is only borne by the patient. Selected centres with required expertise can and will come up with patient pathway designs to mitigate CIT risk sufficiently to ensure safe transplantation. The requirement for a second dose of Imlifidase is only in <10% of reported patients thus far. Therefore, concerns re prolonged CIT in those requiring 2 doses ignores potential benefit in 90% of patients who need only one dose. With nationally agreed careful patient selection, including the antibody thresholds, it is very likely a number of patients could benefit from Imlifidase with very low risk of needing a second dose pre-operatively, ensuring safe transplantation within acceptable CIT thresholds. The draft recommendation document does not explain why a managed market access solution to enable further evidence gathering (evidence of safe use within NHS without impacting on CIT as well as patient and graft outcomes) has been ruled out. It is vital to point out this patient group currently do not have any alternative treatment options other than to wait indefinitely, whilst accruing avoidable morbidity with each passing year on dialysis. As discussed above, the 2019 KoS will not result in a compatible transplant for the vast majority of HSP on the kidney transplant waiting list. A negative recommendation and closure of managed market access pathways effectively condemns HSP to continue to suffer status quo despite a possible treatment option. As a minimum, managed market access to allow data gathering to permit evaluation (both cost effectiveness and operational implementation) within the NHS setting is critical before arriving at any conclusion on potential benefits to the NHS.	Please see section 3.6 of the FAD for the committee considerations. Thank you for this detail. committee discussed the requirement of a second dose further at the third Appraisal Committee Meeting. This is reported in section 3.7 of the FAD. Thank you for noting this. The committee discussions around managed access have been updated in section 3.18 of the FAD.
103	Web comment	North Bristol NHS trust	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? HLA sensitisation and related longer wait-times for a kidney transplant disproportionately affects females (pregnancy related sensitisation) and ethnic minorities (either due to blood transfusions or previous organ transplants). Both these groups are more likely to be sensitised to common Caucasian/Anglo-Saxon HLA types making it much harder to receive a transplant. The long waiter list therefore has a larger proportion of female and non-white ethnicity populations (compared to un-sensitised patients). Recommendation to not support Imlifidase use will have a disproportionately worse impact on female and non-white ethnicity long-waiters for a kidney transplant. The current standard of care is to wait on the national transplant list and it is likely this will result in worsening of health status for women and non-white ethnicity patients compared to men and white ethnicity patients.	Comment noted. Thank you for this detail. The committee considered these issues raised, along with comments from other stakeholders in its decision-making. The committee further discussed these issues at the third Appraisal Committee Meeting. Its discussions are reported in section 3.16 of the FAD.

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104	Web comment	NHS Blood and Transplant	**3.2: People who are highly sensitised wait longer for a suitable donor kidney than those who are not sensitised** The recent changes to the UK renal organ allocation system (Implemented Sept 2019) were designed to meet some of the challenges faced by highly sensitised patients awaiting transplantation. Historically these patients have waited for a period of time far greater than those patients who are unsensitised or moderately sensitised and were therefore unable to realise the health and experience benefits a transplant would bring. In some cases where patients are very highly sensitised the only option to proceed to transplant prior to changes in the organ allocation system was to perform a HLAi transplant. The changes to the renal allocation system in 2019 (and the use of the UKNKSS) have had a positive impact upon the chances of highly sensitised patients awaiting transplant, with many highly sensitised patients receiving a transplant. However, a small number of very highly sensitised patients (cRF 100%) still face significant challenges in terms of access to transplantation. Using the NHSBT ODT kidney reaction frequency calculation tool (Calculators - ODT Clinical - NHS Blood and Transplant) it is possible to determine the number of potential compatible donors from the last 10,000 UK donors. Using such tools, assessment of some highly sensitised patients reveals that none of the last 10,000 donors would be considered compatible. Indicating that without performing a HLAi transplant these patients will remain untransplantable - despite the changes to organ allocation systems and use of the UKNKSS. A recent publication examines this challenge within the United Network of Organ Sharing (UNOS) within the US. Schinstock, CA, Smith, BH, Montgomery, RA, et al. Managing highly sensitized renal transplant candidates in the era of kidney paired donation and the new kidney allocation system: Is there still a role for desensitization? Clin Transplant. 2019; 33:e13751. https://doi.org/10.1111/ctr.13751Sincerely, This paper identifies a finding within the US that patients with a CPRA of >99.9% may still benefit from a desensitisation program. A similar analysis in the UK would be of benefit – however given that changes in the organ allocation system in the UK came into place less than 6 months prior to the start of the Covid-19 pandemic sufficient data may not be available. However, use of the kidney reaction frequency tool by individual H&I laboratories indicates that a small group of patients may still require a HLAi to proceed to transplant as compatible donors are not within the UK donors pool.	Comment noted. Thank you for providing this information and references. The committee considered these issues along with feedback from other consultees in its decision-making at the third Appraisal Committee Meeting.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

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[vi] Kjellman C, Maldonado AQ, Sjöholm K, Lonze BE, Montgomery RA, Runström A, et al. Outcomes at 3 years post-transplant in imlifidase-desensitized kidney transplant patients. Am J Transplant. 2021.

[vii] NHSBT Data provided to Hansa. July 2021

[viii] Krishnan et al. HLA Antibody Incompatible Renal Transplantation: Long-term Outcomes Similar to Deceased Donor Transplantation. Transplant Direct. 2021 Aug; 7(8): e732.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 1 April 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Hansa Biopharma
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Name of commentator person completing form:	[redacted]

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Comment Number	Comments
1	Executive Summary: Hansa ACD Response 1. **Has all of the relevant evidence been taken into account?** o The imlifidase 3 year follow up trial data is robust, relevant and should not be disregarded for appraisal decision making purposes. The efficacy and safety of imlifidase are consistent, irrespective of the subgroup imlifidase enables the transplantation. See Comment Number 10 o The Post Approval Efficacy and Safety (PAES) study and its potential for UK data collection should not be disregarded for this appraisal, particularly as Guy's, Leeds and UHCW have already been selected as PAES study trial centres. See responses in See Comment Number 16 **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** o Hansa engaged and gathered feedback from 15 HLAi clinical experts in eight transplants centres across England, Wales and Northern Ireland to ensure that committee recommendations were in line with NHS clinical practice of kidney transplantation for highly sensitised patients. Feedback received is incorporated into this response. o The potential risk of longer cold ischaemia time (CIT) and the potential consequence of organ wastage is overestimated and needs to be put in the appropriate clinical context. The Committee's recommendation rests on the concern that imlifidase use leads to unacceptable CITs and organ wastage. Hansa disputes this, on the basis of imlifidase clinical trial data which shows no kidneys were discarded due to CIT, or for any other reason. The trial data also shows that nearly all patients will only require one imlifidase infusion and rigorous selection of recipients and donors in line with proposed eligibility criteria, as well as appropriate delisting of antigens should further negate the need for a second imlifidase infusion. In addition, all transplant experts we have spoken to indicated that although they acknowledge that imlifidase will lengthen CIT in most cases, this is not a barrier for use on imlifidase See Comment Number 8 o The rates of AMR seen across imlifidase clinical trials are in line with what is expected in the proposed population and HLA incompatible kidney transplantation. See Comment Number 11 **3. Are the recommendations sound and a suitable basis for guidance to the NHS?** o Imlifidase is an innovative technology that provides substantial and distinctive benefits that may not be captured by measuring health gains such as providing hope for a group of patients that currently have no hope of receiving a transplant. Therefore, the Committee's recommendation is not aligned with NICE Principle 8. See Comment Number 3

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	○ The committee's concerns regarding the opportunity cost for non-sensitised patients are not in keeping with the principles of the KOS which is designed to balance equity and utility. Deceased donor (DD) kidneys are a finite resource, and any future imlifidase patient is already part of the pool of patients waiting for this finite resource, and as such should be treated equitably, based on their position on the waiting list and therapeutic options available. The negative impact for non-sensitised patients is a delayed kidney transplantation (by a few days to a few weeks), not a denied kidney transplantation. Whereas imlifidase enables transplantation of patients who currently have no chance of kidney transplantation, despite recent changes in the Kidney Offering Scheme (KOS). Therefore, the committee's recommendation is not aligned with NICE Principle 9. See Comment Number 9 and 12 **4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** ○ Imlifidase is a step-change in treatment in deceased donor kidney transplantation. implementation should not be a barrier for providing patients an innovative treatment option such as imlifidase, and whose only option is to remain on long-term dialysis which has a significant negative impact on healthcare costs, morbidity, mortality and quality of life. Therefore, not recommending imlifidase does not align with NICE principle 8. See Comment Number 15 ○ NHSBT modelling suggests that the changes to the KOS will improve but never completely resolve the inequity of access for highly sensitised patients. Therefore by not recommending imlifidase, an opportunity is removed to help improve equity of access to kidney transplant for female and highly sensitised patients, which is not aligned with *NICE Principle 9 … our guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged. See Comment Numbers 12 and 14*
2	ACD Section 1 – Why the Committee made these recommendations – PRIORITY RESPONSE • **ACD Statement: "**The clinical evidence was limited and had a short follow up. There is a lack of long term evidence to show the benefits of imlifidase." **Hansa response:** For further information see Comment Number 10 • **ACD Statement: "**Using imlifidase might substantially increase the time from a kidney being donated to the transplant taking place." **Hansa response:** For further information see Comment Number 8

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	• **ACD statement: "**The changes to the UK Kidney Offering Scheme in 2019 have improved access for people who are highly sensitised to HLA. These people might now have improved access to a suitable matched kidney without imlifidase." **Hansa response:** For further information see Comment Number 12
3	ACD Section 3.1 Renal replacement therapies while waiting for a kidney transplant can have a substantial effect on quality of life • **ACD statement:** "The committee recognised that people who are on dialysis, especially for a long time while waiting for a kidney transplant, have reduced quality of life. These people would prefer a transplant if a suitable donor kidney was available." **Hansa response:** Imlifidase is an innovative technology that provides substantial and distinctive benefits that may not be captured by measuring health gains such as providing hope for a group of patients that currently have no hope of receiving a transplant. Therefore the committee's recommendation goes against NICE Principle 8 *NICE aims to support this innovation by encouraging interventions that provide substantial distinctive benefits that may not be captured by measuring health gain (that is, the estimated QALYs gained).* Additionally, this statement does not fully reflect the feedback provided by the Kidney Research UK statement at the 2nd Committee Meeting and the true burden of dialysis: "If I was a dialysis patient knowing I would never have a transplant and never get away from dialysis I would feel life was pretty pointless, particularly as I got older and probably had secondary heath issues. I think I would feel futile, angry and I am sure thoughts of suicide might even play on my mind. Transplant gives opportunity for longer, healthier and potentially more fulfilling life. But all hope can be stolen if you are told you can't have a transplant because it will be rejected." Dialysis impacts patient lives every day in a significant way. Dialysis drives patients' day to day (diet, fluid intake, dialysis procedure itself), and hinders their ability to live their lives as they want to (holidays, family planning, etc.) These daily constraints have a profound impact on patients' mental health and wellbeing. According to clinicians and patient associations we have spoken to, many fully informed patients are willing to accept a higher level of transplant risk in order to be able to once again experience life without having to be tethered to dialysis three times every week, even for a short period of dialysis-free time. And only having hope that a transplant might be possible may change their life outlook significantly.
4	ACD Section 3.2. People who are highly sensitised wait longer for a suitable donor kidney than those who are not sensitised • **ACD statement:** "This is because this creates the opportunity of either directed donation transplant or transplant through the UK Kidney Living Kidney Offering Scheme."

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	Hansa response: Correction required: amend "Living Kidney Offering Scheme" to "UK Living Kidney Sharing Scheme" or "Kidney Offering Scheme", as appropriate • **ACD statement:** "Since 2019, the number of people in this group getting transplants has increased (see Comment Number 8). The committee concluded that before this change, people who are highly sensitised waited much longer on average for a kidney transplant from a deceased donor, compared with people who are not sensitised." **Hansa response:** Please see response for See Comment Number 12 for further information
5	ACD Section 3.3. People who have waited a long time for a transplant may not be well enough to have one by the time a suitable donor is found • **ACD statement:** "Or they may attempt to use a novel desensitisation approach like plasma exchange to remove the HLA antibodies." **Hansa response:** Desensitisation protocols such as plasma exchange are of variable efficacy and take weeks to complete. They are therefore not an option for a deceased donor transplantation in HS patients, which is the indication for imlifidase.
6	ACD Section 3.4 Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people • **ACD statement:** "Some people who had imlifidase in the trials also had a more intensive regimen of immunosuppression drugs after transplant than is currently used in the NHS for transplants without imlifidase. The committee concluded that imlifidase could give some people who are highly sensitised access to a kidney transplant sooner, but that some of these people may need more intense immunosuppression afterwards." **Hansa response:** Post-transplant immunosuppression is standard practice for UK centres offering HLAi transplantation in the UK. The difference between UK and Swedish/US clinical practice was not considered to be a valid reason to prevent patients receiving imlifidase in initial study visits for Guy's, Leeds and UHCW which are the UK centres in the imlifidase PAES study. Importantly, although some of the imlifidase patients will require a more intensive immunosuppression regimen, the alternative for these patients is to remain on dialysis indefinitely which has substantial morbidity, mortality and quality of life impacts.[1]
7	ACD Section 3.5. The proposed population might be appropriate but needs to be considered in the context of current NHS clinical practice **ACD statement: "**They noted that the proportion of deceased donor kidney transplants going to people with a CRF of 100% had doubled from 2% to 4% in the first year of applying the new UK algorithm and this showed evidence that patients

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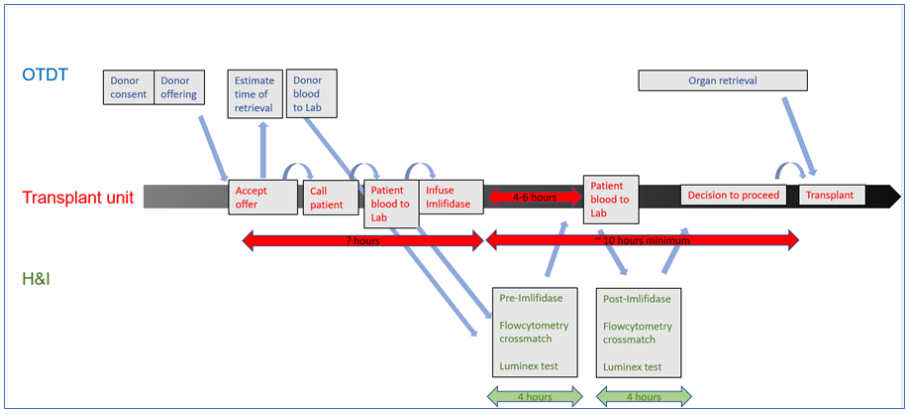
	are doing better since the criteria was changed. But, despite this there are still people who would only be able to have a transplant if imlifidase were to become available." **Hansa response:** To ensure consistency throughout the ACD, we recommend this statement is added into ACD Sections 1. 3.2, 3.11 where it is stated that the current KOS has increased the number of highly sensitised patients getting transplants "But, despite this there are still people who would only be able to have a transplant if imlifidase were to become available." For further information please see Comment number 12
8	ACD Section 3.6. The proposed treatment pathway likely underestimates the impact on cold ischaemic time of the donor kidney – PRIORITY RESPONSE • **ACD statement:** "In that pathway, the estimated cold ischaemic time varied between 10 to 24 hours, depending on the number of imlifidase infusions and number of crossmatch tests needed." **Hansa response:** This statement does not quantify how unlikely it is for the CIT to reach the upper bounds of this range in imlifidase-enabled transplantation. In imlifidase clinical trials, 93.5% (43/46 patients) of imlifidase enabled transplants had a crossmatch conversion after 1 dose. Of the patients that required two imlifidase infusions, [redacted]. Rigorous selection of recipients and donors in line with proposed eligibility criteria, as well as appropriate delisting of antigens should further negate the need for a second imlifidase infusion.[redacted] The ERG's proposed pathway uses 6 hours as the turnaround time for a crossmatch test. Centres which we have spoken to say that they have labs on site, and that the turnaround time could routinely be as low as 2-4 hours. There are also scenarios whereby imlifidase-enabled transplants can be performed without any increase in the CIT whatsoever. Such an instance is set out in the schematic below, as constructed by Professor Briggs, Director, H &I Lab, NHSBT, Birmingham. 

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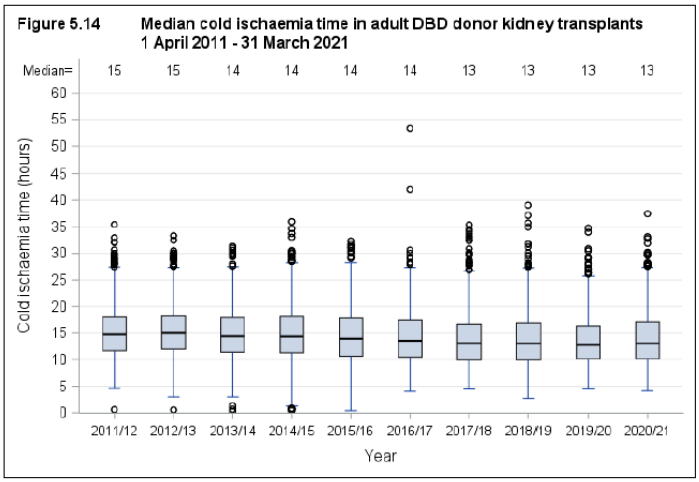
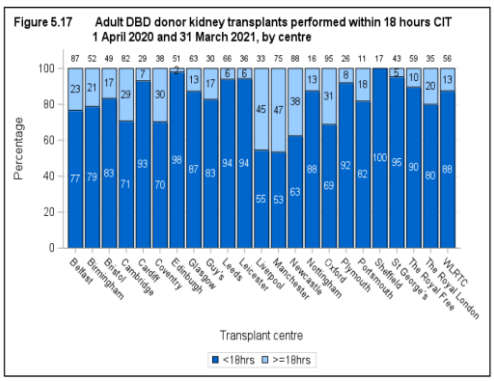
- **ACD statement:** "A time of more than 24 hours would mean the donated kidney effectively becomes unusable for transplant."

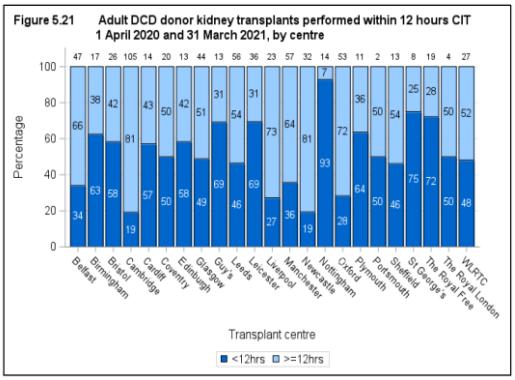
  Hansa statement: This statement is inaccurate. UK clinicians consulted have reported that they regularly transplant kidneys with a CIT of 24 hours or over. Kidneys do not become automatically unusable past the 24-hour mark. [2] The NHSBT annual report states "Evidence indicates that the outcome is only adversely effected when CIT is longer than 20 hours, although many deceased donor transplants with a CIT of more than 20 hours have been very successful."[3]

  In the most recent NHSBT Annual Report on Kidney Transplantation, [3] it is shown that though CIT has fallen a little over the years, transplants are still being performed with over 24 hours CIT. See graph below.



The NHSBT Annual Report[3]also shows there is considerable variation across centres in the proportion of adult DBD kidney transplants that have been performed within 18 hours of CIT. Indeed, there are centres where almost 50% of transplants surpass this threshold.





- **ACD Statement:** "The clinical experts said that the potential of a second imlifidase infusion would add an unacceptable amount of time to the life of the kidney."

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Hansa response: This was not the view shared by the clinicians Hansa consulted at 8 transplants centres across the UK. In relation to the imlifidase clinical trial data, no kidneys were discarded due to CIT (despite the mean total CIT in the 3 year follow data being 21.0 hours which includes organ retrieval and transport to the transplanting hospital), or for any other reason, in the imlifidase clinical trials.
In addition, the Post Approval Efficacy and Safety study is planned to be conducted at 3 centres in the UK: Guy's, Leeds and UHCW. Initial study visits have taken place at all these sites and none of the clinicians involved have raised concerns that a second infusion would increase the CIT to an unacceptable time period.
The transplant MDT will continually assess the benefits and risks of proceeding with the transplantation, including the CIT as well as many other variables. If the imlifidase-enabled kidney transplantation cannot take place due to an excessive CIT, the kidney will not be discarded.
NHSBT have a mechanism called the Fast Track Scheme which is designed to optimise the utilisation of kidneys available for transplantation through simultaneous offering to previously declined, difficult to place kidneys to a number of centres who had opted in to receive such offers. It would be possible for NHSE&I to implement more measures to further minimise this risk, such as the provision of a backup patient. This will be for NHSE&I to decide with NHSBT and the potential imlifidase MDT.

- **ACD statement:** "Centres used in the clinical trial were not based in the UK and the committee acknowledged there could be important differences between these centres and NHS practice which could lead to differing cold ischaemic times. These centres might have been well placed for short cold ischaemic times, by providing high numbers of transplants and donors close-by. But The committee had not seen evidence that a similar result could be achieved in UK clinical practice."
  Hansa statement: As indicated by numerous clinical experts, including three of the NICE clinical experts in their statements, the results from the imlifidase clinical trials can readily be extrapolated to the UK setting. Careful selection of donors, recipients and transplant centres, as well as refining the treatment pathway at the designated imlifidase centres can considerably help optimise results from imlifidase-enabled transplants.
  A consideration from the study data is the difference in CIT between DD patients from the US and those from Europe. See table below. In Europe, all DD patients were transplanted in Sweden. In this Swedish cohort there were no occurrences of delayed graft function. As might be expected, largely for geographical reasons, [redacted].
  For the UK, we would expect the better comparator cohort be the EU/Swedish cohort. It is worth clarifying that CIT calculated in our clinical trial started at organ retrieval and included transport to transplanting hospital.

	Mean	sd	median	25% IQR	75% IQR	Max

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All (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
US (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
EU (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

- **ACD statement:** "Treatment would likely be focused in 4 specialist centres across the country but would need a tendering process to establish which centres could be involved."
  Hansa response: CIT for an imlifidase-enabled transplantation will be further managed as a result of the NHSE&I suggestion of choosing specialist centres which have robust and efficient protocols in place for cross-match testing and on-site laboratories. We look forward to further working with NHSE&I and clinicians on this topic

9

ACD Section 3.7. Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised – PRIORITY RESPONSE

- **ACD statement:** "The committee recognised that the opportunity created by ensuring people who are highly sensitised are treated equally and fairly would need to outweigh any additional costs and any benefit loss created for people who are not highly sensitised, to reflect all costs and benefits."
  Hansa response: This statement also goes against NICE Principle 9: Aim to reduce health inequalities. Hansa disagrees that the equity benefit for highly sensitised patients should outweigh the benefits loss for those who are non-sensitised. The current KOS is not designed to maximize utilities, rather to balance equity and utility. Deceased donor (DD) kidneys are a finite resource, and it is universally true that when any patient receives a DD kidney, there is another patient who doesn't and remains on the waiting list. Any future imlifidase patient is already part of the pool of patients waiting for this finite resource, and as such should be treated equitably, based on their position on the waiting list and therapeutic options available. The concept of maximizing health benefits in kidney transplantation in NHS was recently researched and published. The authors came to the conclusion that "This approach (QALY maximation) yielded the most QALYs for transplant recipients but also resulted in a notable decrease in access to transplantation for older patients. Although the QALY maximization approach made more efficient use of a limited number of kidneys, it resulted in greater inequity in terms of both access to transplantation and the distribution of QALYs between transplant recipients and patients who remained on the waiting list" [4]
  Implementation of imlifidase would align with the KOS objectives as the proposed eligible population is already prioritised by the KOS (as they have Tier A status). See Comment Number 12 for further information.
  In addition, the concept of opportunity cost would in this case mean a comparator outside the imlifidase licensed indication, namely non-sensitised patients, and therefore should not be assessed within this NICE technology appraisal.

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	• **ACD Comment: "**Stakeholders explained that any donor kidney used with imlifidase could have been used for someone else with much lower costs, better outcomes and equal related savings from avoiding dialysis. Because the clinical and cost effectiveness would be lower for some transplants using imlifidase, this could result in a loss of health benefit and increased costs overall for the healthcare system. " **Hansa response:** Imlifidase enables equity of access to kidney transplantation for a small subgroup of patients (see response to section 3.11) who demonstrate graft survival outcomes similar to other patient populations routinely transplanted (e.g. diabetics, FSGS, IgA nephropathy).[5] If the opportunity cost drove decision-making in transplantation, such patients, as well as smokers and elderly patients, would no longer be transplanted. This would go against NICE Principle 9. ○ **ACD Statement: "**Any decision should take account of the opportunity cost that the kidney will be unavailable for other people on the waiting list who are not sensitised**."** **Hansa response:** Non-sensitized patient not receiving a kidney transplant in this situation will likely only experience several weeks delay in kidney transplantation and certainly would not be denied kidney transplantation altogether. By contrast, an imlifidase transplant is the only route to enable transplantation for a small subset of patients with no alternative other than long-term dialysis with substantial morbidity, mortality and quality of life impact.[1] To help quantify this point we have roughly estimated the time it would take for a subsequent offer to be received for a non-imlifidase patient. The latest NHSBT activity report shows that in the year ending April 2021, the median waiting time for a kidney transplant in the UK was 633 days. There were a total of 3,525 patients on the waiting list on 31/3/2021, and in the year ending March 2021 1,790 DD kidney transplants were carried out. Assuming that in the same year [redacted] patients had been transplanted with imlifidase, the impact for the next patient matched to the same organ would be, on average 3.5 days (10 / 1,790 = 0.56%, 633 x 0.56%) = 3.5 days. This should be rounded up to 1 or 2 weeks to account for variation in daily transplantations. By contrast, those patients receiving a transplant with imlifidase would previously have had, little to no prospect of a transplant.
10	ACD Section 3.8. The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS (cf similar drugs for rare diseases) – PRIORITY RESPONSE • **ACD statement: "**The ERG considered that the quality of data beyond the original trials was limited." **Hansa response:** The imlifidase 3 year follow up trial data is robust, relevant and should not be disregarded for appraisal decision making purposes. The indication for this appraisal is classed as rare therefore the trials are consequently small in numbers. Imlifidase was studied in 46 transplanted patients, which for Phase 2 development in orphan diseases is by no means limited.

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	The significant unmet medical need in our licensed indication supported EMA's decision to grant a conditional marketing authorisation based on this same Phase 2 data. Hansa recognizes that the evidence pack will be further strengthened when the Phase 3 PAES study is conducted (including 3 UK centres). However, the efficacy and safety of imlifidase were deemed enough to grant conditional marketing approval, and the indicated patients currently have no access to kidney transplantation and their only prospect is to remain on long term dialysis which has a significant negative impact on healthcare cost, mortality and quality of life.[1] Our 3-year data published last year is in fact the longest-term clinical trial data in the area of highly sensitised kidney transplantations.[6] This makes our trial data highly relevant, extremely important and not to be disregarded for appraisal decision purposes. At the time of HTA decision it is not uncommon to only have 3 years of follow up data available. The uncertainty is diminished by the fact that the efficacy and safety of imlifidase are consistent, irrespective of the subgroup imlifidase enables the transplantation.
11	ACD Section 3.9. Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm (cf likelihood of not receiving a transplant whatsoever) – PRIORITY RESPONSE • **ACD statement: "**The committee considered that there was a high rate of antibody mediated rejection (40%) in the company's original clinical data." **Hansa response:**. AMR rates are higher in incompatible transplantation than in standard transplantation. This is one of the reasons that compatible transplantations are the preferred solution. For patients who cannot benefit from compatible transplantation, there are still, in most cases, substantial benefits with incompatible transplantation compared to dialysis, despite the higher AMR rates incurred. In the recently published 3-year imlifidase follow up data, the overall incidence of AMR was 38%, with the majority of these episodes taking place in the first month following transplantation.[6] None of the AMRs lead to graft failure or death. Clinicians consulted on this have consistently stated that this AMR rate is in line with what is expected in clinical practice when carrying out HLA incompatible kidney transplants, many disagreeing with the figure of 10% for occurrence of AMRs in the highly sensitised population. This figure is more aligned to the incidence witnessed in the compatible transplantation setting.
12	ACD Section 3.11. Data shows that some people for whom imlifidase might be suitable already have access to transplants – PRIORITY RESPONSE • **ACD statement** "…and concluded that some people for whom imlifidase might be suitable will already have access to transplants." **Hansa response:** This conclusion contradicts the statement said in Section 3.5 – please see Hansa response above

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	This conclusion also goes against NICE *Principle 9. Aim to reduce health inequalities: …..So our guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged.* The new KOS has increased chances of a transplant for highly sensitized patients as NHSBT data shows that the proportion of transplants for patients with cRF>99.5% in the UK went from 2% of total transplants performed prior to Sept 2019 (implementation of the new KOS) to 4% in the year following. However, patients with a cRF> 99.5% still currently represent approximately 10% of the waiting list. In addition, NHSBT modelling suggests that the changes to the KOS will never completely resolve the inequity of access for this patient population.[7] These patients face the prospect of remaining on long-term dialysis which has substantial negative impact on health, cost and quality of life.[1] The proposed imlifidase eligibility criteria are aligned with this small subset of transplant patients identified in the NHS BT data as being most unlikely to be transplanted and are also prioritised within the current KOS (as they all have Tier A status).
13	ACD Section 3.12. Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain • **ACD statement: "**It concluded that not everyone who has imlifidase goes on to have a kidney transplant, but the exact proportion is uncertain." **Hansa response:** The assumption accepted by the ERG and used in economic model was using the robust clinical trial data available and should not be discounted (see Comment Number 10). The uncertainty is further diminished by the fact that the efficacy and safety of imlifidase are consistent, irrespective of the subgroup imlifidase enables the transplantation.[6]
14	ACD Section 3.18. Specific consideration needs to be given to people who have become highly sensitised through pregnancy • **ACD statement:** "Clinical experts noted that one of most common causes for a person to be highly sensitised with HLA is previous pregnancy." **Hansa response:** It has been demonstrated that imlifidase enables transplantation for highly sensitised patients, regardless of the cause of their sensitisation. NHS BT data clearly show that in the cohort of most highly sensitised patients, females have a lower probability of being transplanted than males, and constitute a higher proportion of this population.[7] In turn, imlifidase is currently the only treatment option to enable kidney transplantation for a small subset of highly sensitised patients such as this. Therefore, not recommending imlifidase goes against NICE *Principle 9. Aim to reduce health inequalities: …..So our guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged.*

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15	ACD Section 3.19. Imlifidase could provide a step-change in treatment but there are challenges/alterations for implementation - PRIORITY RESPONSE • **ACD statement:** The committee concluded that imlifidase could provide a step-change in treatment but there are challenges for implementation. **Hansa response:** Not recommending imlifidase goes against *NICE Principle 8. Support innovation in the provision and organization of health and social care services*. Imlifidase is a step-change in treatment in deceased donor kidney transplantation, and when Hansa consulted with UK clinical experts across the country, the potential challenges in its implementation are considered to be readily manageable. Any potential implementation challenge needs to be assessed within the appropriate clinical context (see Comment Number 8). Irrespective, implementation should not be a barrier for providing patients an innovative treatment such as imlifidase which is the only option to enable transplant for a small subset of highly sensitised patients. Imlifidase has been reviewed as part of the EMA PRIority MEdicines (PRIME) programme which supports medicines that may offer a *major therapeutic advantage* for patients without treatment options. EMA identified Idefirix as an Outstanding Contribution to Public Health, awarded to only 12 medicines approved in 2020 that represent significant progress in their therapeutic area. Imlifidase was granted conditional marketing authorisation as there is a clear unmet need for a small subset of highly sensitised patients who remain unlikely to be transplanted despite the moderate success of the currently kidney offering scheme. The proposed imlifidase eligibility criteria are aligned with this small subset of transplant patients identified in the NHSBT data as being most unlikely to be transplanted and are also prioritised within the current KOS (as they all have Tier A status). The only prospect for these patients is long-term dialysis, which has a significant negative impact on healthcare costs, morbidity, mortality and quality of life.[1] See Comment Number 12
16	ACD Section 3.20. Managed access agreement is not appropriate • **ACD statement:** It considered that the ongoing studies are unlikely to provide meaningful additional data for committee decision making. • **Hansa response:** Hansa disagrees with this statement. The Post Approval Efficacy and Safety study will collect relevant outcome (e.g. graft outcomes) and safety data (e.g. AMR and CIT) relevant to this appraisal and will be conducted in selected UK hospitals.
17	ACD Section 1 – Why the Committee made these recommendations - PRIORITY RESPONSE

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

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	• **ACD statement: "**The cost-effectiveness estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources."
	Hansa response: Please see comment number 19 for the current base case estimates which demonstrates that imlifidase is a plausibly cost-effective treatment options across all base case scenarios. Hansa acknowledges that this is an exceptional appraisal for the ERG and NICE committee as this the first technology appraisal in this innovative drug class within this rare indication of significant unmet need. Although it cannot be directly utilised for decision making purposes within this current appraisal, Hansa would like the committee to note that NICE have recognised this exceptionality within the proposed review of NICE methods, giving additional weight to health benefits in the most severe conditions, a health inequalities modifier and opportunities for handling uncertainty. In addition, Hansa would like to reiterate current NICE methods guidance regarding factors which should be specifically accounted for when assessing the effective use of NHS resources. Section 6.3.3 of the guidance outlines the following factors:
	  • The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure – see Comment Number 15
	  • Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21) – see comment number 3

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18

Section 3.13. Graft survival projections from iBox are highly uncertain so a hazard ratio should be applied to account for this

- **ACD Statement: "**It concluded that graft-survival predictions were highly uncertain because of data from a very small data sample informing long-term extrapolations." **Hansa response:** Hansa's base case assumption for graft survival projections remains the 3-year follow up data. We believe that this is the most relevant data set to model graft survival. Please see comments number 10 for further information on rationale for not disregarding this data set for decision making purposes.
  It is widely accepted that long-term allograft survival is impacted by multiple variables including (but not limited to) medication non-adherence, donor graft quality, ischemic reperfusion injury, co-morbid conditions and original cause of kidney failure. Therefore, it is difficult to compare the potential outcomes of patients who receive an imlifidase-enabled kidney transplant to any other cohort than the true standard of care, which are patients currently awaiting a compatible organ offer while on dialysis.
  Hansa does however accept that NICE needs to validate evidence sources used for decision making. Therefore, Hansa recommends the iBox graft survival extrapolation is a relevant scenario to validate the 3 year-follow up base case against. When comparing the 5-year and 10-year survival estimates from the two most recent UK data sources published (NHSBT Annual report data[3] and a paper published last summer by Krishnan et al[8] at University Hospital Coventry and Warwickshire (UHCW) hospital on incompatible transplantations) with the iBox projections, 5-year and 10-year graft survival rates are all higher than the iBox extrapolations. It can be concluded that there is no robust rationale for applying a 0.9 hazard ratio (HR) to the iBox extrapolation. On this basis, we request that the NICE/ERG base case is updated with the 0.9 HR removed, and that the '3 year follow up' scenario is factored into committee decision making.

Source	Five year Graft Survival	Ten year Graft Survival
NHSBT 2007-2009, DCD [3]	0.86	0.75
NHSBT 2013-2015, DCD [3]	0.86	-
NHSBT 2007-2009, DBD [3]	0.85	0.74
NHSBT 2013-2015, DBD[3]	0.87	-
Krishnan et al, 2021, HLAi cohort[8]	0.85	0.70
Imlifidase iBox	[redacted]	[redacted]
Imlifidase iBox, HR = 90%	[redacted]	[redacted]
All imlifidase extrapolations – 3 year follow up data	[redacted]	[redacted]
UTT imlifidase extrapolations – 3 year follow up data	[redacted]	[redacted]

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19	Section 3.16. The most plausible estimates are above what NICE normally considers cost effective and there are substantial issues with implementation – PRIORITY RESPONSE • **ACD statement: "**The company's deterministic base-case ICER was £27,754 per QALY gained and its probabilistic ICER was £29,210 per QALY gained. The ERG's deterministic base case was £37,525 per QALY gained and its probabilistic ICER was £38,971 per QALY gained. **"** **Hansa response:** The ERG and Hansa assumptions for the cost effectiveness model are all aligned, with the exception of the graft survival assumption (see (comment number 18). [redacted]. This revision allows imlifidase to demonstrate plausible cost effectiveness for both the deterministic and probabilistic base case scenarios listed within the ACD. Please see below the Hansa base case and alternative scenarios (differing in terms of graft survival assumption). Hansa added a scenario which uses the Krishnan et al graft survival data, for the rationale see Comment Number 18. Please also find in the Appendix the revised deterministic results, probabilistic scenario analyses and results. - Hansa base case ICER (graft survival based on 3-year data) = £20,725 per QALY - Hansa alternate scenario (graft survival based on iBox without HR) = £25,214 per QALY - Hansa alternate scenario (graft survival based on Krishnan et al data) = £18,723

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

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Appendix: Cost Effectiveness Results

Hansa deterministic results including the ERG preferred model assumptions accepted by Hansa (i) Allow 5% of SoC to receive 'no dialysis' (ii) Increase number of crossmatch tests to 2.42 (iii) Allow patients in SoC arm to receive a transplant at cycle 0; and graft survival based on the 3 years data extrapolation: [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Imlifidase and transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,725
Dialysis	217,575	8.10	5.92				

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Hansa base case probabilistic results (3-year data extrapolation): [redacted]

	Costs (£)			QALY			ICER (£/QALY)
	Imlifidase and transplant	**Dialysis**	**Incremental**	**Imlifidase and transplant**	**Dialysis**	**Incremental**	
Reference case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,725
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,009
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,595
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	78,873

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

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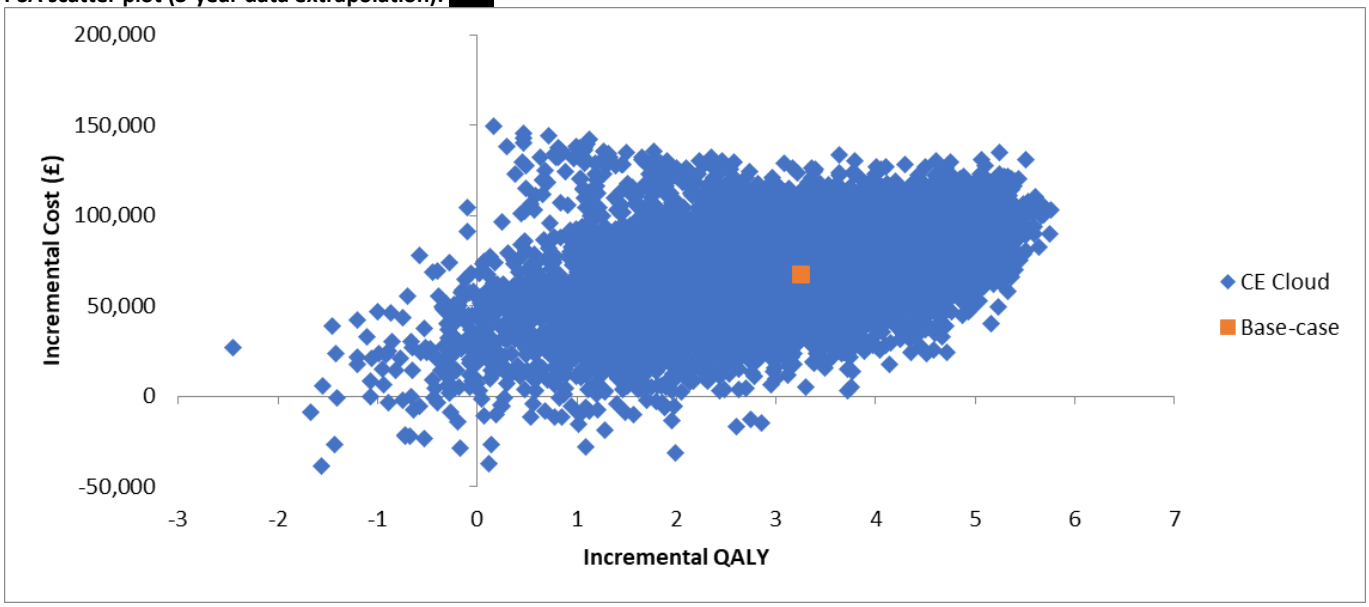
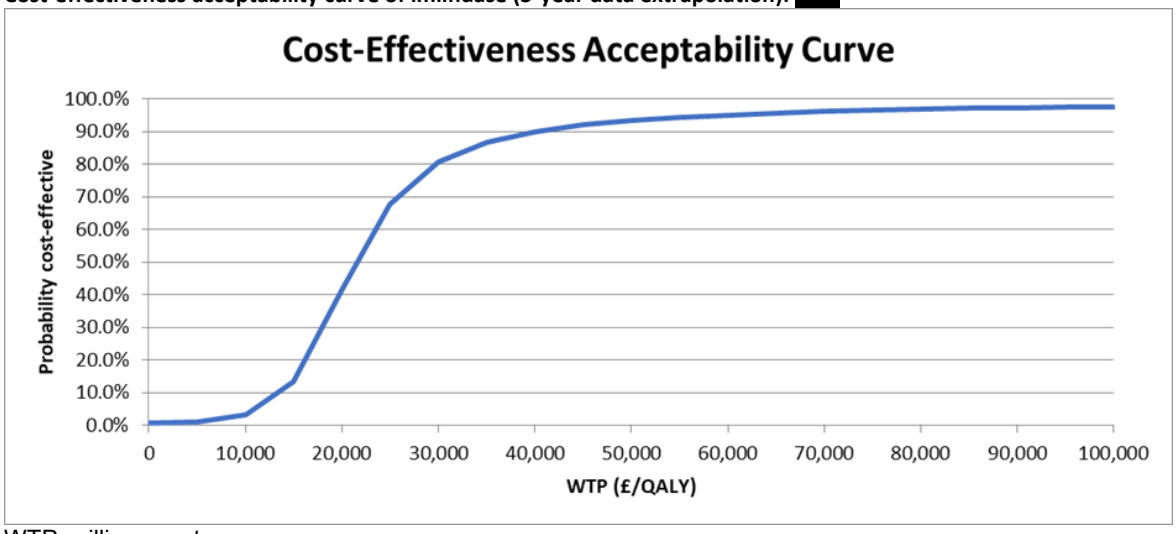
PSA scatter plot (3-year data extrapolation): [redacted]



CE cost-effectiveness.

Cost-effectiveness acceptability curve of imlifidase (3-year data extrapolation): [redacted]



WTP, willingness to pay.

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

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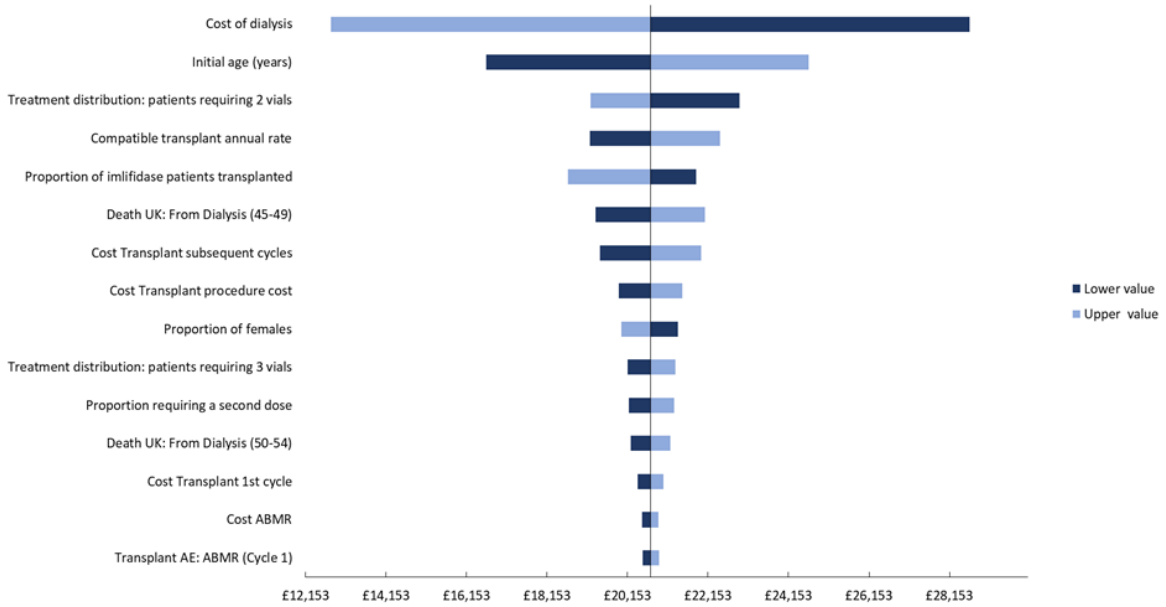
Results of the one-way sensitivity analysis (3-year data extrapolation): [redacted]



AMBR, antibody-mediated rejection.

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

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Results of the scenario analyses (3-year data extrapolation[redacted]

	Δ Costs (discounted), £	Δ QALY (discounted),	ICER, £	Difference from baseline, %
Reference Case	[redacted]	[redacted]	20,725	
Scenario 1: Time horizon, 10 years	[redacted]	[redacted]	55,132	166
Scenario 2: Time horizon, 20 years	[redacted]	[redacted]	24,933	20
Scenario 3: Graft loss extrapolations, iBox	[redacted]	[redacted]	25,214	22
Scenario 4: Graft loss extrapolations, All	[redacted]	[redacted]	21,014	1
Scenario 5: Graft loss extrapolations, Krishnan et al 2021	[redacted]	[redacted]	18,723	-10
Scenario 6: Survival extrapolations, UT	[redacted]	[redacted]	30,880	49
Scenario 7: No caregiver disutility	[redacted]	[redacted]	21,396	3
Scenario 8: Caregiver disutility (Nagawasa et al. 2018)	[redacted]	[redacted]	21,115	2

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; UT, unlikely to be transplanted.

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

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Hansa deterministic results including the ERG preferred model assumptions accepted by Hansa (i) Allow 5% of SoC to receive 'no dialysis' (ii) Increase number of crossmatch tests to 2.42 (iii) Allow patients in SoC arm to receive a transplant at cycle 0; and graft survival based on the iBox data (no hazard ratio): [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Imlifidase and transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,214
Dialysis	218,894	8.04	5.87				

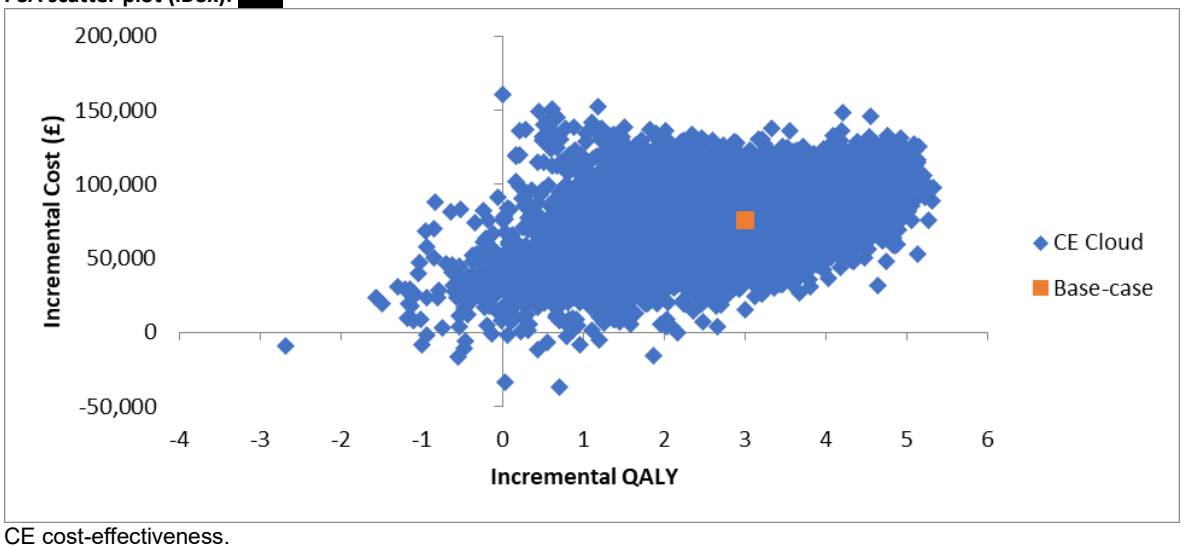
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Hansa base case probabilistic results (iBox): [redacted]

	Costs (£)			QALY			ICER (£/QALY)
	Imlifidase and transplant	**Dialysis**	**Incremental**	**Imlifidase and transplant**	**Dialysis**	**Incremental**	
Reference case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,214
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,504
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,696
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,607

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

PSA scatter plot (iBox): [redacted]



CE cost-effectiveness.

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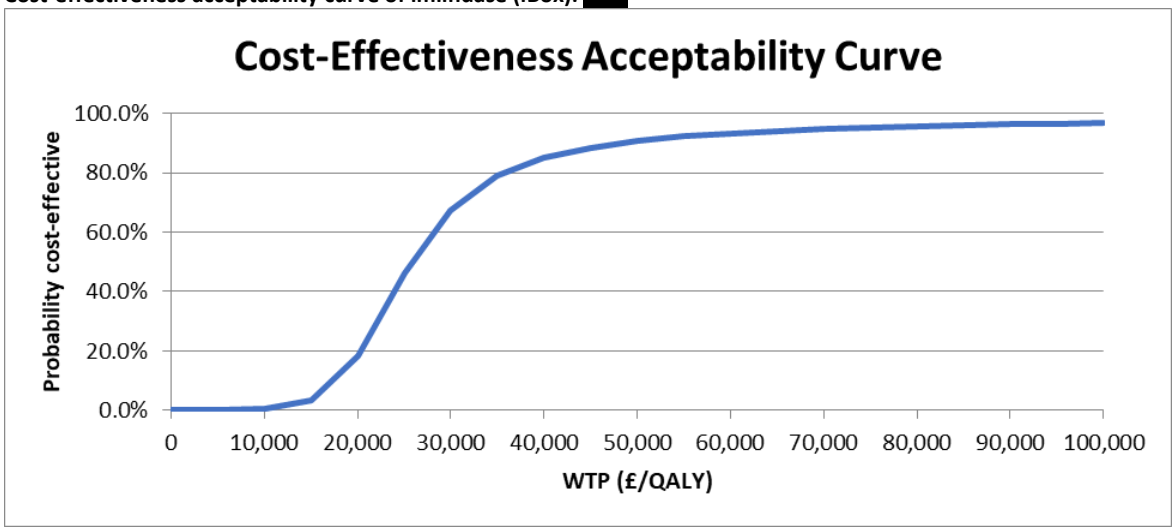
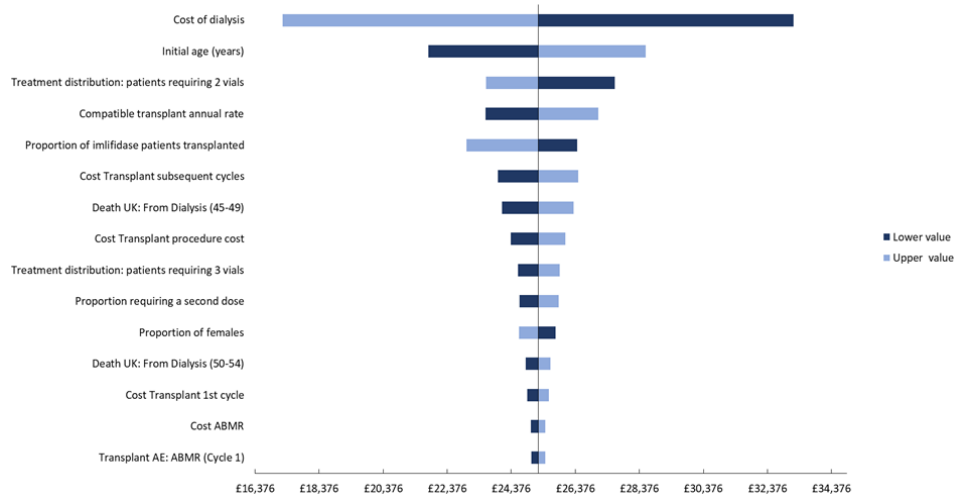
Cost-effectiveness acceptability curve of imlifidase (iBox): [redacted]



WTP, willingness to pay.

Results of the one-way sensitivity analysis (iBox): [redacted]



AMBR, antibody-mediated rejection.

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Results of the scenario analyses(iBox): [redacted]

	Δ Costs (discounted), £	Δ QALY (discounted),	ICER, £	Difference from baseline, %
Reference Case	[redacted]	[redacted]	25,214	
Scenario 1: Time horizon, 10 years	[redacted]	[redacted]	65,062	158
Scenario 2: Time horizon, 20 years	[redacted]	[redacted]	30,986	23
Scenario 3: Graft loss extrapolations, UTT	[redacted]	[redacted]	20,725	-18
Scenario 4: Graft loss extrapolations, All	[redacted]	[redacted]	21,014	-17
Scenario 5: Graft loss extrapolations, Krishan et al. 2021	[redacted]	[redacted]	18,723	-26
Scenario 6: Survival extrapolations, UT	[redacted]	[redacted]	39,187	55
Scenario 7: No caregiver disutility	[redacted]	[redacted]	26,035	3
Scenario 8: Caregiver disutility (Nagawasa et al. 2018)	[redacted]	[redacted]	25,692	2

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; UT, unlikely to be transplanted.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

References

[1] Tonelli et al. Systematic Review: Kidney Transplantation Compared With Dialysis in Clinically Relevant Outcomes. American Journal of Transplantation 2011; 11: 2093–2109

[2] Summers, D.M., et al., *Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study.* Lancet, 2013. **381**(9868): p. 727-34.

[3] NHS BT Annual Report on Kidney Transplantation. Published September 2021. kidney-annual-report-2020-21.pdf (windows.net)

[4] Li et al. Equity–Efficiency Trade-offs Associated With Alternative Approaches to Deceased Donor Kidney Allocation: A Patient-level Simulation. Transplantation 2020;104: 795–803).

[5] O'Shaughnessy et all . Kidney Transplantation Outcomes across GN Subtypes in the United States. J Am Soc Nephrol. 2017 Feb;28(2):632-644. doi: 10.1681/ASN.2016020126

[6] Kjellman C, Maldonado AQ, Sjöholm K, Lonze BE, Montgomery RA, Runström A, et al. Outcomes at 3 years post-transplant in imlifidase-desensitized kidney transplant patients. Am J Transplant. 2021.

[7] NHSBT Data provided to Hansa. July 2021

[8] Krishnan et al. HLA Antibody Incompatible Renal Transplantation: Long-term Outcomes Similar to Deceased Donor Transplantation. Transplant Direct. 2021 Aug; 7(8): e732.

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British Transplantation Society Response to Appraisal Consultation Document (ACD) – 'Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease'

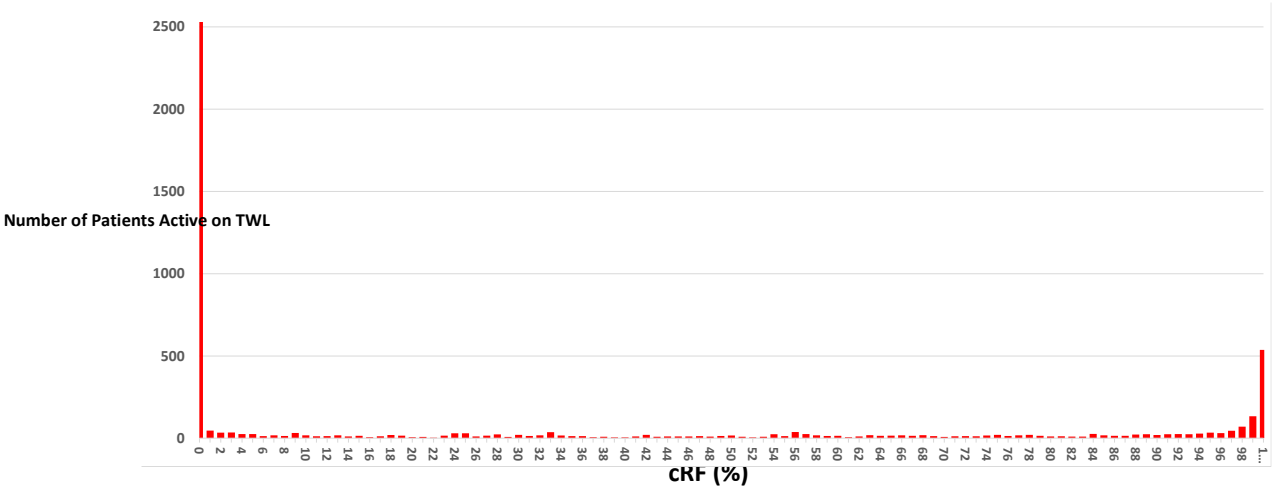
Dear NICE

Thank you for including the British Transplantation Society as a Consultee in the appraisal process for Imlifidase. We have studied the ACD, and have a number of comments. We continue to support the use of Imlifidase in selected highly sensitized kidney transplant candidates, and hope the points below are helpful in reviewing the proposed negative recommendation.

Sections 3.1 – 3.4

We are pleased that the committee recognizes both the important advantages of transplantation (life expectancy, quality of life, freedom from dialysis, and important psychosocial benefits) but also the challenges in successfully transplanting highly sensitized patients.

Sensitization (immunologic memory against non-self human leucocyte antigens -HLA) is quantified by detecting antibodies against HLA in a serum sample. The calculated reaction frequency (cRF) is the percentage of the last 10,000 deceased against which a transplant candidate has anti-HLA antibodies. A cRF of 0% means there are no significant anti-HLA antibodies (the patient is not sensitized against any HLA), whereas a cRF of 100% means that the patient has anti-HLA antibodies against >99.5% of these 10,000 donors. The distribution of cRF amongst the transplant waiting list (in February 2020, immediately pre-COVID) is shown below:



This is important because of 4938 active wait-listed patients half have a cRF of 0%, most of the rest a cRF distributed between 1 and 98%, **but a large minority have a CRF of 99 or 100%** (671 patients – 13.5% of the total active waiting list). The majority of these have a cRF of 100% (537 patients – 10.9% of the active waiting list).

Ideally all kidney transplants would be antibody-compatible – that is the recipient has no antibodies against any donor HLA. However for those with a cRF of >99% compatible donors are a rare event – that is why these very highly sensitized patients wait many years for the offer of a kidney (or are never offered a kidney). These patients accumulate on the waiting list leading to the skewed distribution of cRF as shown above.

Section 3.5 - Current pathway for cRF >99% patients.

The ERG and committee have reviewed the current approach to the extreme inequity in access to transplantation for these patients, which is referred to throughout the ACD. This approach was introduced in September 2019 following a substantial revision of the National Kidney Offering Scheme operated by NHSBT:

- cRF 100% patients are allocated to Tier A of the allocation algorithm.
- Donated kidneys are first matched to Tier A, and allocated if antibody compatible to any Tier A patient (prior to 2019 this prioritized allocation was only given to patients who had already been on the waiting list for 7 years)
- In the first year of the 2019 allocation scheme 63 kidneys were transplanted into Tier A patients – about 10% of the total, although of course new patients are being added to Tier A all the time.
- So even with this new allocation algorithm the median waiting time for a Tier A patient is likely to be >5 years (compared to the median national waiting time of 536 days – substantially less than 2 years).

Accordingly these very highly sensitized patients remain profoundly disadvantaged. Moreover, both patients from ethnic minorities and women are over represented in Tier A – the former because of an excess of blood group B patients, and the latter because of HLA sensitization caused by pregnancy (discussed in Section 3.18 of the ACD)

Access to transplantation for these patients may be increased by allowing antibody-incompatible transplants. Many transplant centres already allow 'low risk' AIT – those where the recipient has antibodies against donor HLA but at a relatively low level. In general the donor specific antibodies (DSA) are of insufficient titre to cause a positive cellular cross match (that is a cross match performed by flow cytometry (FC) or by complement dependent cytotoxicity (CDC)).

However, most of the cRF>99% patients have multiple high level antibodies that would cause a positive cross match against an incompatible donor. Performing a transplant against a positive cross match carries a high risk of early, severe antibody-mediated rejection and graft loss. A positive cross match can be overcome by treatments to remove antibody from the blood (for example plasma exchange), but multiple treatments over several days are needed. Many centres have used antibody-removal protocols to allow planned antibody-incompatible living donor transplants, but these protocols are not possible to allow an incompatible deceased donor transplant because of the short time between the offer of a kidney and the transplant (hours).

Imlifidase offers, **for the first time**, the opportunity of an antibody incompatible deceased donor kidney transplant. The manufacturer of Imlifidase has provided data from several uncontrolled studies demonstrating that Imlifidase is able to remove DSA from the circulation (and thus convert a positive cross match to a negative cross match) in the majority of treated patients (52 out of 54 treated patients – 96.3%). Despite a significant incidence of antibody-mediated rejection (as DSA are resynthesized weeks – months after Imlifidase treatment), medium-term outcomes are good despite the necessarily limited data and uncontrolled nature of the trials.

The ACD raises a number of specific points which we have addressed directly:

Section 3.6 – The proposed treatment pathway likely underestimates the impact of cold ischaemic time of the donor kidney

There are a number of inaccurate assumptions in this section:

- *Before an Imlifidase infusion can be started a cross match test is needed*. This is partly correct, but the cRF>99% patients on the waiting list considered eligible for Imlifidase have an extensive history of HLA antibody screening. Thus, when a kidney is offered the cross-match result can be determined at once, using contemporary HLA antibody screening results – a 'virtual cross match'. Importantly, kidneys are usually offered before the retrieval operation has taken place. Accordingly, the patient can be admitted to the transplant unit and the virtual cross match reported *before* any cold ischaemic time has been accrued.
- As soon as the kidney is retrieved, and the retrieving surgeon has confirmed that it is transplantable, the Imlifidase infusion can be started
- Six hours after the infusion a further HLA antibody screen is needed to conform that the DSA have been eliminated from the circulation – a test that takes about 4 hours.
- So from retrieval to reporting of the post-Imlifidase HLA antibody screen would result in a very reasonable cold ischaemic time of <12 hours. During this time the kidney would be in transit from the donor hospital, and the patient readied for the transplant operation – for example receiving dialysis. These processes take place concurrently, not sequentially.

- *The committee considered that the variation in timings could mean there is a risk that the kidney is wasted.* We consider this outcome to be so unlikely that it should not be part of the ACD. As outlined above, the process of administering Imlifidase and performing a post-treatment cross match is not associated with excessive cold ischaemia. There is good evidence from the UK that, for DBD kidneys, a cold ischaemic time of up to 24 hours is not associated with adverse outcomes[1]. Even if the Imlifidase treatment is not successful, and the kidney needs to be re-allocated, then there are robust systems already in place to do so in a timely fashion – the 'Fast Track' system.
- In fact it is common for kidneys to be transported to a transplant centre that, often many hours after retrieval, determines that the kidney cannot be transplanted:

    - Kidneys offered as part of a kidney + pancreas transplant, but with the pancreas deemed unsuitable for transplantation.
    - An unexpected positive cross match
    - Medical complications in the recipient

- We believe that concerns over cold ischaemic time and the theoretical risk of a kidney being wasted are unfounded.

Section 3.7 – Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are non-sensitized.

We do not believe this concern is justified. Quite clearly a donated kidney can only be transplanted into one patient, and so the other 5000 or so patients on the waiting list necessarily do not receive that kidney. This is the case every time a kidney is allocated – whether to a sensitized or non-sensitized patient. All patients are listed on a single national waiting list, and under the current pathway sensitized patients are profoundly disadvantaged. The use of Imlifidase seeks to correct this inequity. The argument that a non-sensitized patient may somehow be disadvantaged makes no sense at all.

Particularly important is the consensus view that those cRF>99% patients considered for Imlifidase should have been wait-listed for a period of time (at least 2 years) before becoming eligible for Imlifidase. This approach:

- Allows for a reasonable opportunity that a compatible kidney is allocated to cRF>99% patients
- Means that cRF>99% patients will already have accrued waiting time greater than the national median and thus likely ranked above non-sensitized patients in the allocation algorithm whether or not Imlifidase is used.

The committee is also concerned that '**the clinical (and cost) effectiveness would be lower for some transplants using Imlifidase'.** It may well be true that graft survival following a high risk incompatible transplant facilitated by Imlifidase is likely less good than if the same kidney were used as a compatible transplant. But this is a poor argument. There are many other patient characteristics that predict less good outcomes – for example the recipient's age, or presence of diabetes – but we do not discriminate against those patients by offering kidneys only to young fit recipients likely to have the best outcomes. We believe that it is unfair to discriminate against cRF >99% patients on the grounds of inferior outcome – particularly when the only alternative is a life on dialysis.

Section 3.8 – The available outcome data is currently too short term to decide whether Imlifidase can be used in the NHS.

Section 3.9 – Some antibody-mediated rejection is expected but people who are highly sensitized may have better outcomes if they wait for a match in the new algorithm

Section 3.11 – Data shows that some people for whom Imlifidase might be suitable already have access to transplants

It is correct that long-term data on outcomes is limited, but given the highly specialized nature of antibody-incompatible transplants this is almost inevitable. Never the less the 3-year outcomes reported by Kjellman in Imlifidase-treated patients[2] are at least as good as those in antibody incompatible live donor transplants in the UK[3,4]. In all of these reports antibody-mediated rejection is inevitable – close to 40% in the highest risk recipients (those with sufficient DSA to give rise to a positive CDC cross match).

We agree with the ACD that cRF>99% patients should have been on the deceased donor waiting list for sufficient time to be allocated a compatible kidney if such an offer is realistic. The quoted figure of 31.4 % of these patients receiving a compatible kidney seems reasonable – likely realized within 3-4 years waiting in Tier A (see comments on Section 3.5 above). But this still leaves the majority of cRF>99% patients without a transplant.

Certainly the introduction of Imlifidase in the UK should be a careful and nationally coordinated process, including:

- Mandated waiting time in Tier A to allow the opportunity of a compatible transplant
- Careful selection of acceptable but incompatible HLA specificities aiming to avoid transplants with strong positive CDC cross match, thus reducing the incidence of AMR and improving long-term outcomes[3,4].
- Avoiding patients with extreme levels of DSA thus reducing (even eliminating) the risk of a patient receiving Imlifidase but not achieving clearance of DSA and thus not proceeding to transplant.

We believe that the robust, centralized, and national transplant system operated by NHSBT lends itself perfectly to the careful introduction of Imlifidase in the UK, and to the collection of data that will quickly inform the most appropriate use of Imlifidase in this very challenging group of patients.

Section 3.12 – Not everyone who has Imlifidase treatment goes on to have a kidney transplant, but the exact proportion is uncertain.

This does not seem a reasonable concern. 52 out of 54 Imlifidase-treated patients in the series reported by the company did receive a transplant – 96.3%. Careful patient selection (see above) may further reduce the risk of a non-proceeding transplant.

Section 3.14 – The number of cross match tests will likely be higher than 1 and should be included in the economic model.

The robust detail of HLA antibody screening for wait-listed patients in the UK is described in the comments on Section 3.6. This applies to all wait-listed patients – cRF>99% or not. A post-Imlifidase test (cellular or virtual cross match) is absolutely required, but for the majority of patients this would be just one cross match. Careful patient selection (see above) would negate the need for a second Imlifidase infusion (in any case a rare event – only 3 of the patients in the various series reported). In any case, the cost of a cross match is negligible compared to that of transplantation in general and Imlifidase in particular.

Section 3.19 – Imlifidase could provide a step-change in treatment but there are challenges in implementation.

In many ways this is the central issue. We hope that, in the points above, we have outlined how Imlifidase can be effectively introduced in the UK taking advantage of our coordinated national transplant program. We believe we have addressed the practical concerns raised in the ACD and encourage the committee to revise their recommendation.

References

1. Summers *et al* (2015). Kidney donation after circulatory death (DCD): state of the art. *Kidney Int* **88**, 241-249
2. Kjellman *et al* (2021). Outcomes at 3 years post-transplant in Imlifidase-desensitized kidney transplant patients. *Am J Transplant* **21**, 3907-3918
3. Higgins *et al* (2011). Human leucocyte antigen antibody-incompatible renal transplantation: excellent medium-term outcomes with negative cytotoxic crossmatch. *Transplantation* **92**, 900-906
4. Pankhurst et al (2017). The UK national registry of ABO and HLA antibody-incompatible renal transplantation: pre-transplant factors associated with outcome in 879 transplants. *Transplant Direct* **3**, e181

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 1 April 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Kidney Association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have received: 1. Study support from Cheisi pharmaceuticals and Oxford Immunotech 2. Consultancy fees from Natera and Cheisi I will be due to receive speaker fees from Sanofi I also plan to meet with Hansa pharmaceuticals to discuss my current study in antibody mediated rejection (this has not happened yet)

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NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 1 April 2022. Please submit via NICE Docs.

Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	On behalf of the UKKA, overall, I believe the provisional recommendation and guidance to be sound. Notably: a. Assessment of the impact of the KOS 2019 now needs to be considered in the clinical and cost effectiveness model. As a single centre, over 15% of our kidney transplant recipients transplanted since the change have a cRF>85%. It should also be considered that the full impact of the 2019 KOS probably has been hindered by the COVID pandemic during 2020 (pre-vaccination), when transplant units were closed or selective in their recipients. b. Cost effectiveness has to include the use of additional immunosuppressive therapies, e.g IVIG and rituximab which are not routinely used in the UK. c. The long-term outcome data for Imlifidase is not available, but early rejection in 'HLAi' is recognised to be associated with the development of chronic antibody mediated rejection and premature graft loss. I note the early rejection rates provided as evidence occurred in just under <50%. d. The agent will be best assessed as part of a study to best determine its role in the UK
2	The evidence review has focused on deceased organ transplant recipients alone where the overall benefit for organ utilisation will be neutral as alternatively the organ would be used in a low-risk recipient, in whom the transplant survival is probably going to be greater, and certainly cheaper. I think it would be important to consider the benefit of imlifidase in highly sensitised patients who fail to get matched via the UK living kidney sharing scheme. Data suggests that the indication for the majority of pairs to enrol in the scheme is due to HLA incompatibility, and not all get matched. Certainly, the likelihood of getting matched if not paired after a few attempts is low. The alternative for these people is to proceed with the HLAi transplant or wait for a deceased donor organ. Due to limited effectiveness of HLAi currently in the UK, most wait for a deceased donor if they cannot find an alternative living donor. A model where these recipients are offered imlifidase, thereby 'freeing' up a deceased donor organ for someone without a living donor would provide greater cost effectiveness.
3	The review highlights the concern of prolongation of cold ischaemic time (CIT) to enable the full evaluation of antibody status post imlifidase. The review group have also raised concern that the CIT maybe so long that there is risk that the organ would be rendered unusable. A lot of centres in the UK, have access to machine perfusion technologies for organ optimisation prior to implantation. If, imlifidase was used in the deceased donor setting, this technology could be adopted to preserve the organ during the cross-match assessment.
4	The lack of long-term efficacy data negates concern that NICE may not be fulfilling its commitment to 'promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.'
5	

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NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 1 April 2022. Please submit via NICE Docs.

6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Response to Imlifidase ACD prepared on behalf of the NHS England and Improvement Clinical Reference Group (CRG) on Transplantation issues by [redacted]

We reviewed all of the documents including all the committee papers (ID1672 [redacted]) but this response refers to the ACD prepared for consultation with consultees.

We were pleased to see that the ACD recognised the very positive potential benefits of Imlifidase including:

- *"Renal replacement therapies while waiting for a kidney transplant can have a substantial effect on quality of life"* (page 5)
- *"People who are highly sensitised wait longer for a suitable donor kidney than those who are not sensitised"* (page 6)
- *"People who have waited a long time for a transplant may not be well enough to have one by the time a suitable donor is found"* (page 7)
- *"Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people"* (page 7)
- *"The proposed population might be appropriate but needs to be considered in the context of current NHS clinical practice"* (page 8)
- *"But, despite this [introduction of the new UK organ offering algorithm] there are still people who would be able to have a transplant if Imlifidase were to become available" (page 9)*

We would like to comment on the reasons that the ACD concludes that the therapy cannot be recommended:

Initial Comments.

Regarding the first point above, it should be recognised that a kidney transplant not only transforms patients' quality of life but **also** a significant improvement in life expectancy compared with long-term dialysis (and this is greater, the younger the patient is).

We disagree with the company's suggestion that patients should be offered this therapy after waiting for at least two years. As the ACD points out, the latest NHSBT kidney offering scheme introduced in 2019 was modelled and designed to improve access to HSP. However, this scheme has not had an opportunity to demonstrate if this modelling correctly predicted the improved access to deceased donor kidneys for highly sensitised patients (partly because it has only been in use for just over 2 years but confounded by the Covid pandemic). In our opinion the therapy should be reserved for patients waiting at least four or five years to give time for a potential antibody compatible deceased donor kidney to be offered. However, after four or five years there is a significant increase in cardiovascular morbidity and mortality in patients remaining on dialysis. Initially, only patients falling into Tier A should be offered the treatment.

Specific Comments.

1. *Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised: (page 12)*

and

"Stakeholders explained that any donor kidney used with imlifidase could have been used for someone else with much lower costs, better outcomes and equal related savings from avoiding dialysis"

This is true and important but the HSPs are currently severely disadvantaged. Of course, whenever any patient receives a deceased donor kidney, another patient does not.…all patients (incl HSP) on the active W/L are in a pool…if one patient receives a kidney someone else doesn't…imlifidase recipients aren't ***additional*** to the other patients on the W/L…so we don't understand this argument, especially since the HSPs are already disadvantaged.

2. *The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS*

The outcome data is necessarily short although the three-year data published by Kjellman et al (2021) does demonstrate comparable outcomes to other highly sensitised patients undergoing HLA incompatible transplantation. We appreciate that the inclusion criteria in this published cohort does not include only patients who would fit the proposed use of Imlifidase in the NHS, but we do not believe that a randomised controlled trial is possible. There are considerable data in the literature indicating the benefit of "desensitising" highly sensitised patients compared with those left to wait for an antibody compatible kidney transport, or never being offered one (see 10 below).

We agree that more data are required, and would be acquired if the therapy were adopted. The ERG and the Committee have identified important concerns such as the numbers of patients not proceeding to transplantation after treatment, the potential wasting of a donor kidney, which we think is likely to be very small indeed.

3. *The proposed treatment pathway likely underestimates the impact on cold ischaemic time of the donor kidney*

The ACD states "A time of more than 24 hours would mean the donated kidney effectively becomes unusable for transplant." (page 10). This is untrue for DBD Kidneys (Summers et al 2013[1], which analysed UK NHSBT data). In most cases, the potential highly sensitive patient would be brought to the hospital as soon as the potential donor have been identified. There will be no need to perform a cross match before Imlifidase administration because this would be predicted from the laboratory knowledge of the patient's antibody profile and donor HLA. We envisage that treatment would be given as soon as the donor kidney is retrieved and, in the opinion of the retrieving surgeon, to be suitable for implantation. By the time the kidney arrives at the transplant centre usually, within 8-10 hours, a cross match could be performed and if negative transplantation could follow as soon as theatre is available. Even if a second treatment were necessary in most cases transplantation could proceed at or shortly after 24

hours. In the unlikely event of a repeat positive cross match the kidney could be transplanted into another antibody compatible recipient, who could be brought in as a backup to prevent a further delay in transplantation and increased cold ischemic time.

Reference

Summers, D.M., et al., *Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study.* Lancet, 2013. **381**(9868): p. 727-34.

4. *Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm*

This is true, but patients in the target population (already waiting > 7 yr and highly sensitised or matchability 10 and cRF >99%) are very unlikely to receive an antibody compatible kidney. Although patients with ABMR are likely to have a reduced transplant survival, this can still be many years, reducing cardiovascular morbidity and greatly improving quality of life whilst the transplant is working. Furthermore, although 40% of patients did have ABMR, 60% did not. In the 3 year follow up study of 39 Imlifidase treated patients with positive cross-match, the graft survival was similar-actually 93% ABMR+ and 77% ABMR-, although the patients who suffered ABMR had less good function (eGFR 48.5 ml/min v. 60.5 ml/min).

5. *Data shows that some people for whom imlifidase might be suitable already have access to transplants*

Clearly this is true, but again surely the issue pivots on how long a highly sensitised patient is likely to wait for an antibody compatible kidney and whatever the company's lower estimate is (redacted), even if the 31.44% stands, the vast majority of patients will not get a transplant and, as pointed out above, every year on dialysis adds to the cardiovascular morbidity and mortality.

6. *Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain*

We believe that it is agreed that the vast majority, more than 96% of eligible patients receiving imlifidase ***will*** be transplanted, which seems a small number to exclude its use for the majority.

7. *The number of crossmatch tests will likely be higher than 1 and should be included in the economic model*

"…To account for this the ERG applied the costs of 2.4 crossmatch tests in its preferred base case"

Firstly, this seems excessive. Our understanding is that only 3/46 recipients required a second dose of imlifidase, although 1 received a second dose based on a 2 hr post imlifidase sample although the 6 hr sample was actually negative, so 2/46, <5%. In any case most units would do a crossmatch post-transplant even when the pre-transplant cross match was virtual, so no extra crossmatch and the cost of the crossmatch is tiny in relation to the other costs.

8. *The committee was aware that while there may be better quality of life initially after transplant, overall quality of life for some people after imlifidase and a transplant may be lower compared with the overall population who have a transplant without imlifidase.*

We agree that this MAY be the case, but the correct comparator for the successfully transplanted imlifidase recipient is with patients on long-term dialysis who either never get a transplant or have to wait many years, both of which are associated with much poorer quality of life and shorter life expectancy

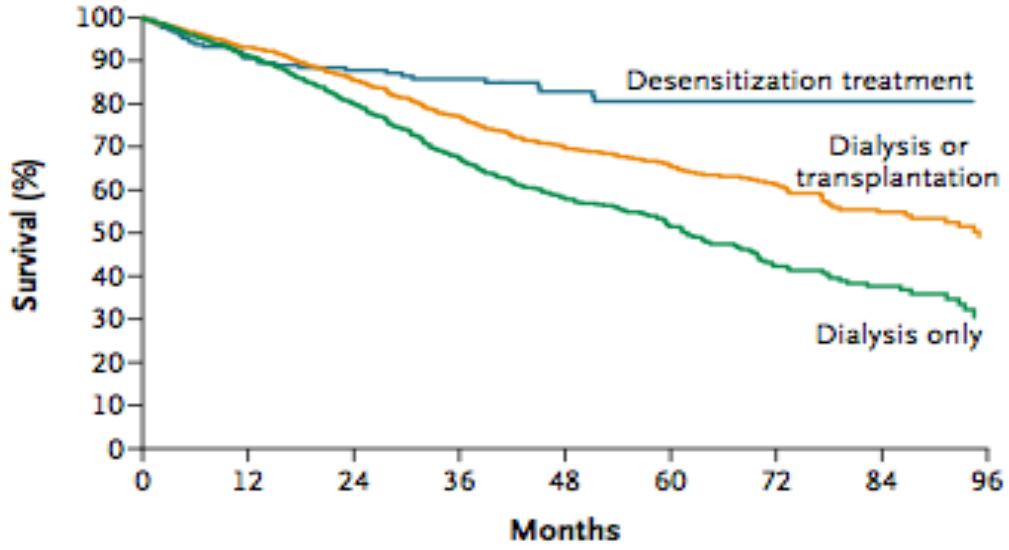
9. *"Evidence for the clinical effectiveness of imlifidase originally came from 4 non-UK based, uncontrolled, open-label studies. The primary outcomes reported on safety and ability to achieve a crossmatch conversion after treatment with imlifidase. For this reason, they had short follow-up times*

that ranged between 64 days and 180 days."

Because the number of patients eligible for imlifidase treatment is small and since "control" patients may wait very many years or never receive a transplant without imlifidase, a controlled trail is not practical. As the Committee & ERG are aware there are now 3-yr outcome data, and the KM plots are flat by 3 yr and this is similar to data on desensitised patients.

10. *"Clinical opinion sought by the ERG suggested that longer-term data beyond 3 years would be needed to better determine clinical outcomes, especially on graft survival and health-related quality of life, for people who have a transplant with imlifidase. The company has planned a phase 3, controlled, non-randomised, open-label study. The committee considered that long-term outcomes reported in this would be critical but that there was currently not enough data available from this study to inform decision making."*

We agree that longer term graft and patient survival are ideally needed but believe that there are data that are applicable in this setting. For example, Montgomery et al who reported on more than 2300 HSP suitable for transplantation. 210 had desensitisation while 1027 remained on dialysis but received a transplant at some stage and 1012 patients were not transplanted by the time of analysis (see figure below). Clearly desensitisation (with prior positive crossmatch) demonstrated superior survival (even if the transplant failed) and the Committee and ERG accept that life with a transplant provides a much-improved quality of life.



No. at Risk									
Desensitization treatment	210	170	143	110	75	58	42	28	14
Dual therapy	1027	854	688	497	321	230	157	96	41
Dialysis only	1012	822	626	419	250	159	93	54	17

Montgomery, R.A., et al., *Desensitization in HLA-incompatible kidney recipients and survival.* N Engl J Med, 2011. **365**(4): p. 318-26.

Final Comments

We note in the ACD acknowledges that “Imlifidase could provide a step-change in treatment but there are challenges in implementation.” (Section 3.19). We believe this is truly a step change innovation that would, if introduced into the NHS, allow a relatively small number of highly disadvantaged patients receive a kidney transplant that they would otherwise be very unlikely to access, improving both quality and quantity of life.

We hope that the NICE committee consider our comments countering reasons why the ACD has, prior to consultation, not recommended its introduction by the NHS and urge revision of the provisional decision.

Comments on the ACD received from the public through the NICE Website

Name	[redacted] (NHS blood and transplant)
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
No. Comprehensive evidence about rejection rates and outcomes for antibody incompatible transplantation is lacking.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I feel the interpretations of clinical effectiveness are not always consistent with all the available evidence.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No, not yet.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
This form of treatment is essentially about equity of access to transplantation where age, gender and race can be associated with being disadvantaged.

General comments
Section 1: The Title of the appraisal consultation document is misleading. The implication is that Imlifidase prevents rejection. Misleading because there are many types of rejection. Imlifidase use is to prevent hyperacute rejection caused be pre-existing donor-specific antibodies. Other types of rejection, such as acute and chronic AMR and ACR should be unaffected by Imlifidase.

1.2: Using imlifidase might substantially increase the time from a kidney being donated to the transplant taking place.
“might substantially increase cold ischaemia time (CIT)” – a process should be designed to avoid this (Peacock et al 2022, IJI). The UK has recently developed crossmatching guidelines designed to minimise CIT. A key principle is to complete testing before the donor organ arrives at the transplant centre. This can be accomplished by using pre-donation blood samples from the donor and virtual crossmatches (VXM). This framework could be used in the context of pretransplant antibody reduction by Imlifidase treatment. The VXM uses existing antibody data, both level and specificity, and an experienced HLA laboratory should be able to assess potential suitability. Donor offering is an early event in the transplant process and an immediate VXM could be used to assess suitability and necessity for Imlifidase use.

3.2: although a small number of people could wait up to 7 years.
It is stated the "a small number of people could wait up to 7 years". This is misleading. Such people are likely to wait more than 7 years and as such this group accumulates on the waiting list. On the W Midlands waiting list (about 10% of UK), for example, there are 36 people who have been waiting for more than 7 years (median of 10.4 years), 33 of whom have a CRF of 100%.

3.4: Because the treatment has a transient effect, antibody levels in the body rise after transplant.
The transient effect of Imlifidase is very similar to that of plasmapheresis used in this context: both are designed to reduce pre-transplant HLA antibodies. Desensitisation by various forms of plasmapheresis has been used in the UK since about 1984. The early rise after the transplant is seen with both forms of treatment. This has been well documented by the Coventry group (plasmapheresis used) and is usually associated with good outcome as in most cases the antibodies fall spontaneously (Higgins et al 2009. Transplantation).

3.5: a CRF of 100%
A CRF of 100% actually covers a range of sensitisations. The CRF of 100% term used in the UK refers to those cases of 99.5% and over. If the CRF is considered to two decimal places the impact of the 2019 allocation scheme is likely to look very different. This can be seen from the USA experience where new allocation scheme based on the same principles (priorities to long waiters and the highly sensitised) was introduced in 2014 (the US calculates CRF, or PRA, to two decimal places). Improved access to donors was seen in those with a CRF between 99.5% and 99.95%, but not in those with a CRF>99.95% (Stewart et al, AJT 16; 1834-1847. 2016). Many of the UK waiting list patients will have a CRF>99.95%, some are 100.00%. A person with a CRF of 99.95% might expect less than one HLA and ABO compatible donor per year; those with a CRF of 99.99%, about one every ten years; those with 100.00%, none. In contrast, someone with a CRF of 99.5% (also called 100% in the UK) can expect around 5 ABO and HLA compatible donors pa.

3.7: The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS
The clinical effectiveness of Imlifidase is about its ability to remove HLA antibody reactivity. This is therefore an alternative to plasmapheresis and in this its effectiveness is proven. There is a mortality risk associated with plasmapheresis (eg fatal hypotension) so Imlifidase is likely to be a safer approach to antibody depletion. Post-transplantation events are more likely to depend on the same factors for Imlifidase treatment as with plasmapheresis desensitisation. Longer term outcomes are therefore likely to resemble those seen with plasmapheresis desensitisation and in the UK there are centres with extensive experience. The largest UK single centre outcomes have been published recently (Krishnan et al 2021) which shows overall good outcomes and how to avoid the higher risk cases.

3.9: Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm

This statement is incorrect. An antibody-mediated rejection (AMR) rate of 40% is consistent with HLA antibody incompatible transplantation in general and is seen with plasmapheresis desensitisation. Imlifidase is not and anti-AMR agent. An AMR rate of 10% would be consistent with a standard risk transplant (antibody compatible). Therefore a 40% AMR rate with Imlifidase treatment is expected.

3.13: Therefore it could be reasonable to assume that graft survival is worse in people who are highly sensitised,

There is good evidence that graft survival is worse in highly sensitised recipients who receive an incompatible kidney (from conventional antibody removal). The risks, though, are not the same for all people and we now understand who are the higher risk cases and who could be excluded (Krishnan et al, 2021). Those with the strongest antibodies, identified by a cytotoxic crossmatch (CDC), due to higher levels and multiple donor-specific antibodies, have a significantly short graft life. Graft survival in CDC negative cases is similar to that seen for conventional transplants.

3.18: It concluded that although people who have become highly sensitised through pregnancy may have poorer clinical outcomes, it is unknown whether there would be additional benefit from imlifidase and further information is needed.

This conclusion does not properly fit the evidence. The issue of being pregnancy-induced sensitisation does need special consideration. Firstly, the sensitisation rate in females is higher than in males, for this reason, with about double the rate of being highly sensitised for females. Secondly, graft survival for CDC positive HLA incompatible females is particularly poor. Thirdly, although the early rejection rate in female CDC negative HLA incompatible transplants is high, the outcome in these cases is good: those with early rejection (within the first two weeks) have a similar graft survival to the rejection-free cases (Krishnan et al, 2021). The crossmatch status will depend on a donor's HLA type, thus there must be access to donor offers, and therefore a potential recipient of Imlifidase, to be able to make this assessment (this of course applies to all potential antibody incompatible candidates). Access to these donors and Imlifidase treatment is therefore likely to restore equity of access to transplantation to those whose high level of sensitisation involves previous pregnancies.

3.18: Imlifidase could provide a step-change in treatment but there are challenges for implementation

The challenges to implementation are probably well-rehearsed and understood in centres experienced in the clinical management of desensitisation - the issues will the same. This appraisal does not seem to have recognised that Imlifidase can be seen to be an alternative to plasmapheresis and is effective where plasmapheresis is inappropriate.

Imlifidase as a form of desensitisation to allow transplantation in highly sensitised people is certainly novel and in that it has proven to be very effective. Pretransplant desensitisation itself is not novel (the world's first cases were performed in the UK in the mid 1980s). However, plasmapheresis is can be less effective than Imlifidase in that very high levels can be refractory to extracorporeal removal, there are certain people for whom plasmapheresis can be a high risk procedure (mortality from hypotension), and it typically requires multiple, successive sessions over many days. Pre-transplant plasmapheresis then is usually not an option with deceased donors. Imlifidase does solve all these three problems.

3.11: The committee accepted this change and concluded that some people for whom imlifidase might be suitable will already have access to transplants. Comment on section: Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain
An analysis based on a rounded-up CRF calculation (ie anything 99.5% and over) would be unreliable in support of this statement.

Name	[redacted] (Belfast Trust HSC NI)
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Yes, although no consideration of live donor kidney transplants, where benefits are greater (longer lasting kidney) and costs less (no opportunity cost for alternate recipient, plus no prolonged cold ischaemic time

Are the recommendations sound and a suitable basis for guidance to the NHS?
No - the 2019 amended deceased donor allocation scheme still fails a sub-group of 100% sensitised recipients. These are often young recipients with a prior failed transplant, who become un-transplantable and die after 10-15 years for co-morbid burden. Imlifidase offers this small cohort a chance for a normal life

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

1.2: Why the committee made these recommendations
In the published literature on imlifidase, no kidneys were discarded for prolonged cold ischaemia. In the UK, the smaller geographic size means

that kidneys are typically transported 100-400 miles; the published studies were carried out in USA, France and Sweden, where transport distances are 100-3000 miles, giving longer ischaemic times.

This concern of ischaemic time does not exist for live donor kidneys, where donor timing can be co-ordinated with negative cross-match (although this is outside market authorisation).

The change in deceased donor allocation in 2019 does make access for sensitised recipients a little better, though in Belfast we still have 5-10% of our waitlist as 100% sensitised with current wait-times of 5-11 years.

The concerns for pricing certainly seem reasonable.

3.4: Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people
This group of sensitised patients will always need more intensive maintenance drug regimens, and more treatments for antibody-mediated rejection. This is the case currently with protocols using plasmapheresis and IVIg to achieve negative crossmatch.

3.5: The proposed population might be appropriate but needs to be considered in the context of current NHS clinical practice
Using only for 99%-100% sensitised patients seems very sensible

3.6: The proposed treatment pathway likely underestimates the impact on cold ischaemic time of the donor kidney
In Belfast we sometimes request a deceased donor blood sample prior to retrieval of organs for sensitised recipients. This allows crossmatch tests (+/- imlifidase) to be given in advance of organ retrieval, allowing reduced ischaemic times.

It might be expected for imlifidase to select kidneys from younger deceased after brain death donors - for these kidneys, ischaemic times up to 36 hours are possible - though admittedly shorter ischaemic time is always better

3.7: Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised
The use of every deceased donor kidney involves an opportunity cost of alternate recipients not transplanted. We already take on lower cost-effective recipients; our diabetic recipients have worse outcomes than average, but we still transplant them. Our sensitised waitlist patients suffer from worst equity of access.

3.8: The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS
The 2021 study of 46 patients provided 3-year follow-up. This timepoint is certainly beyond the area of concern for early graft loss from antibody-mediated rejection.

Although not as good as 10-year data, it would be a shame to wait 10 years to provide access to a worthwhile novel treatment.

3.9: Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm
40% antibody mediated rejection is higher than for a standard immunologic risk transplant, but not surprising in this 99-100% sensitised population with incompatible transplants.

3.16: The most plausible estimates are above what NICE normally considers cost effective and there are substantial issues with implementation
Cost concerns are very reasonable. If younger recipients were recruited, and live donor kidneys which have a longer half-life, then the QALY values would improve

If live donor kidneys are used, there is no opportunity cost of a kidney lost to another waitlist recipient - the recipient provides their own unique kidney which would not otherwise have materialised.

Name	[redacted] (University Hospitals Coventry and Warwickshire)

Comments on the ACD:

Has all of the relevant evidence been taken into account?
It is sad to see that a drug which has the potential to be a game changer for highly sensitised patients, who have been waiting on the transplant list for years without a possibility of a live donor, be denied a place for reasons that could be overcome easily. My response to the points raised by the committee are as follows:

1. Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease:
Imlifidase is not an anti-rejection drug to prevent antibody mediated rejection (AMR). It is used to create a window, wherein the HLA antibodies against the donor are invalidated, so that an antibody incompatible transplant (AIT) can be performed. Therefore, this drug can be compared to the process of plasmapheresis which is used to remove antibodies over a few days to enable live donor antibody incompatible transplantation.

2. People who have waited a long time for a transplant may not be well enough to have one by the time a suitable donor is found:
This statement is absolutely true as evidenced by the recent metanalysis which showed that there is significant patient survival benefit with transplantation compared with dialysis (Chaudhry et al, 2022 BMJ). This is why it is important to transplant even highly sensitised individuals so that their survival is increased (Orandi et al, NEJM 2016, Krishnan et al

Transplant Direct 2021). Additionally, about 45% of the very highly sensitized (>99.5% calculated reaction frequency [cRF]) wait for over 7 years on the waiting list. Drugs like Imlifidase would be the only option to be able to transplant this cohort.

3. Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people:
This should not come as a surprise as Imlifidase only creates a window where in the HLA antibodies are eliminated (or reduced) to enable a transplant. Imlifidase is equivalent to plasmapheresis for live donor AIT. The chances of rejection needing powerful immunosuppressive medications post AIT is about 40% (Krishnan et al, 2021 Transplant Direct; Stegall et al AJT 2009).

4. The proposed population might be appropriate but needs to be considered in the context of current nhs clinical practice:
The criteria of cRF >99%, a matchability score of 10 and on the waiting list for more than 2 years seems a reasonable starting point for consideration of Imlifidase in this group of patients. It is possible that the criteria of inclusion could be expanded to other long waiters with cRFs of >95% and could even include live donor transplantation once the success of Imlifidase is demonstrated in this group of individuals.

5. The proposed treatment pathway likely underestimates the impact on cold ischaemic time (cit) of the donor kidney:
The CIT should start from the time the kidney is removed and not from the time it reaches the centre. Please refer to my detail response below to question 3, point 2.

6. Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised:
Please refer to my detail response below to question 2.

7. The available outcome data is currently too short term to decide whether imlifidase can be used in the nhs: Please also refer to my detailed response below to question 3 point 1. The use of Imlifidase is for eliminating (or reducing) HLA antibodies, similar to procedures like plasmapheresis. Plasmapheresis unfortunately is not possible in deceased donation due to time constraints which affects the CIT. Moreover, there is an increased risk of bleeding intra-operatively due to the unintended removal of coagulation proteins during the process. In addition, the risk of severe hypotension including the associated risk of morbidity (blindness etc) and mortality, precludes many patients from undergoing plasmapheresis and hence the opportunity to have a transplant. High level of antibodies and certain types of HLA antibodies are not easily removed by plasmapheresis. Thus, an intervention like Imlifidase would be the best option for such patients.

8. However, the exact details are confidential and cannot be reported here: This statement by the committee is rather confusing, as the 3-year outcome paper is available in the public domain. Is there any other data that has been confidentially shared which is of significance?

9. Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm:
Though there is no comparator arm in the company's clinical data, many AIT transplants done post-plasmapheresis in expert centres world-wide have shown an early AMR rate in the range of 40% (Bentall et al, AJT 2013; Marfo et al, CJASN 2011, Locke et al AJT 2007). Therefore, the company's AMR rate of 40% with Imlifidase treatment is expected. Despite the high rate of AMR, the long-term outcomes of AIT are very good (Orandi et al, NEJM 2016; Krishnan et al, 2021 Transplant Direct). With regards to the new kidney offer system (KOS) algorithm, please see my detailed response to question 3, point 3 below.

10. A small number of people would not have dialysis before having a transplant with imlifidase:
I agree that it is difficult to estimate the number of such patients. However, this situation is not uncommon especially in individuals whose current transplant is failing but the function is stable enough to not require dialysis.

11. Data shows that some people for whom imlifidase might be suitable already have access to transplants:
This statement is not clear. It is like saying that some patients on deceased donor list might already have access to live donors. However, this would not preclude them from being placed on the deceased donor list as the aim is to give these patients a suitable kidney at the appropriate time so that the benefits of transplantation outweigh the risks of waiting on dialysis. Although the new KOS has allowed more transplants in this very highly sensitised group, 90% of the patients in this cohort are still waiting for a transplant. This is the population who should be considered eligible for Imlifidase.

12. Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain:
This is true with any new intervention as patients could have adverse reactions which cannot be predicted.

13. Graft survival projections from ibox are highly uncertain so a hazard ratio should be applied to account for this:
These prediction models are not necessarily reliable given the complexity of antibody incompatible transplantation.

14. Utility values from li et al. 2017 are an appropriate source for decision making:
It is interesting that the committee has stated that 'after Imlifidase, the overall quality of life may be lower'. This speculation surely should not be a factor in determining whether Imlifidase can be made available for a group

of highly sensitised patients. It is important to remember that Imlifidase is like plasmapheresis and therefore the comparators should be the studies on AIT using plasmapheresis. The alternative for not having a transplant with Imlifidase is to wait on dialysis. Many studies have irrevocably shown that the quality of life on dialysis is poor when compared to transplantation. (Jansz et al, Plos One 2016; Rambod et al, Health Care Management 2011)

15. Specific consideration needs to be given to people who have become highly sensitised through pregnancy:
Please see my response below to question 4.

16. Imlifidase could provide a step-change in treatment but there are challenges for implementation:
Yes, Imlifidase is a potential step-change in the treatment of highly sensitised patients waiting for a transplant on the deceased donor waiting list. The challenges of implementation can be sorted by starting with one or two expert centres and expanding later on according to the demand. Please refer to my detailed response below to question 3, point 4.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
1. Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised:
This statement almost suggests that it is acceptable to let very highly sensitised die on the waiting list. The cost aspects of the drug should certainly be discussed and negotiated with the company. However, the value of the drug in helping the 8-10% of the individuals on the waiting list get a life line cannot be overlooked. The alternative of staying on dialysis with the associated complications and morbidities, also has a considerable impact on the health economy which cannot be discounted.

2. The number of crossmatch tests will likely be higher than 1 and should be included in the economic model:
The number of extra CM test when compared to a standard transplant would be 1. Therefore, the total cost of the CMs should be calculated for 2 CMs and not 2.4.

Are the recommendations sound and a suitable basis for guidance to the NHS?
As mentioned above, the reasons for not recommending this drug are not strong and the issues stated can easily be circumvented.

1) no long-term evidence to show the benefits of imlifidase:
The use of Imlifidase is for eliminating (or reducing) HLA antibodies, albeit for a brief period, which enables an AIT to happen. Thus, Imlifidase should be compared to procedures like plasma exchange, immunoadsorption, double filtration plasmapheresis etc which are used to reduce the level of HLA antibodies to create a window of opportunity. Therefore, the outcomes of transplant post-Imlifidase is very likely to be similar to those post

plasmapheresis. As the centre of expertise with the maximum number of complex AIT transplants post plasmapheresis, our results show that long term graft and patient survival is similar to first-time deceased donor transplantation in the U.K. (Krishnan et al, 2021, Transplant Direct). The overall patient survival of AIT transplantation was 95%, 89%, and 81%; and graft survival was 95%, 85%, and 70% at one, five, and 10 year, respectively, which is similar to the first-time deceased donor transplantation in U.K. Orandi et al, 2016 NEJM, showed that the patient survival of the highly sensitised patients if transplanted was 77% at 8 years post-transplant. The three-year study from the company has also shown similar outcomes of 90% patient survival and 84% graft survival. The UK Renal Registry annual report 2018, showed that 10-year survival of all patients between the age groups of 18 to 64 years, on renal replacement therapy (which includes dialysis and transplants), was 55%. To improve the survival outcome of highly sensitised patients on the transplant waiting list who do not have a live donor, Imlifidase is the only option available currently.

2)imlifidase could increase the risk of donor kidneys becoming unusable:

Yes, CIT could potentially increase beyond 12-18 hours; however, there are easy ways to circumvent this issue and ensure that the donor kidney is not wasted with the use of Imlifidase.

i) Imlifidase would potentially be used only in highly sensitised patients who would have had prior delisting of selected antibodies. The quantification of these antibodies can be made available from the most recent blood sample. If this blood sample is less than a month (or even two) old, then one can be certain that the crossmatch (CM) is very likely to remain unchanged. Thus, a virtual CM would be more than sufficient to decide if the patient could be given Imlifidase. A wet CM should also be requested simultaneously to compare the quantification with a wet CM that would need doing 6 hours post infusion. This would ensure the CIT is not unduly increased.

ii) The company has suggested that a few patients may need a second dose of Imlifidase if the CM is not converted to negative after the first dose. The second dose could potentially make the CIT much longer as another CM needs to be done after 4-6 hours after the first dose of Imlifidase. As the process of CM takes about 4 hours, an additional dose could add an extra 8-10 hours as the same process has to be repeated again. Looking at the company's previous publications, it seems that less than 5% of the patients had required a second dose. As one dose is sufficient to convert to a negative CM for 95% of the highly sensitised patients, the protocol should be changed to only one dose as a norm. However, if need be, a clause can be added to include a second dose in case of a persistent positive cross match IF the benefits of the second dose far outweighs the risks of increasing CIT and potential DGF.

iii) It is not an uncommon practice to get a potential recipient as a backup during deceased donation in some units. This practice can be made

mandatory if a patient is being considered for Imlifidase. The backup recipient can be transplanted if:

a) the first patient has an adverse reaction to the drug

b) after the first dose the cross match remains positive. However, experienced centres in AIT may proceed to transplant the first patient at a low level of antibodies i.e- Cytotoxic negative but flow positive or cytotoxic negative, flow negative but luminex positive

c) on very rare occasions after the second dose if the CM does not become negative

iv) As use of machine perfusion is increasing currently, one could possibly consider machine perfusion for kidneys intended for highly sensitised patients eligible for Imlifidase. Kruszyna et al Transplant Proceedings 2021, showed that hypothermic machine perfusion significantly reduced delayed graft function and compensated for extended storage time.

3) changes to the uk kidney offering scheme (kos)2019 have improved access for people who are highly sensitized and hence they may have improved access without imlifidase:

According to the data from NHSBT, there has been an increase of 10% transplantation in these highly sensitised patients after the change in the KOS. It is well known that patients who are very highly sensitized i,e >99.5% cRF comprise about 10% of the waiting list. Even if the new KOS has increased the transplantation rate by 10% which equates to 1% of the very highly sensitised cohort, what happens to the remaining 9% (i,e 90% of this group)?

Stewart et al AJT, 2016 showed that the rate of transplant in the group who have greater than >99.95% cRF is significantly less than those with lower cRF, despite the changes in their allocation policy. They also showed that there is a bolus effect where by the rate increased initially but reduced later. Moreover, the highly sensitized group will be increasing constantly due to the use of expanded donor criteria and fast track organs. As Metzger et al pointed out in AJT 2003, the use of these organs would result in increasing sensitization as these grafts do not last as long as standard deceased donor grafts. Every new patient joining in Tier A in the new KOS, would further disadvantage the existing highly sensitised group.

Thus, though the KOS has improved the chances of a transplant in this highly sensitised group, the need for a drug like Imlifidase still remains very high to achieve reasonable equity in this group of patients.

4) uncertainty about how imlifidase would be integrated into the existing transplant process:

AIT is a very highly specialized field requiring a lot of expertise and intricate understanding. In addition, the success of the programme depends on the ability of the tissue typing laboratory and the renal transplant unit to function seamlessly as one unit. The use of Imlifidase requires even more coordination. Therefore, if one or maximum two centres with AIT expertise are made as national centres for Imlifidase, the process of integrating the use of Imlifidase into the existing transplant process would become much easier and would also yield the best possible outcomes. This process of

learning can subsequently be adapted to include other centres, if need be according to the demand.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
As mentioned in my response to question 2, the recommendation regarding the drug unduly disadvantages the 8-10% of the highly sensitized population on the waiting list who do not have a potential live donor to be entered on to the paired exchange. Drugs like Imlifidase are their only chance of getting a kidney transplant currently.

Specific consideration needs to be given to people who have become highly sensitised through pregnancy:
Pregnancy increases the chances of patients becoming very highly sensitised and hence these patients would benefit from Imlifidase. However, all patients who are very highly sensitised should be considered equally eligible for Imlifidase.

Name	[redacted] (North Bristol NHS trust)

Comments on the ACD:

Has all of the relevant evidence been taken into account?
The 2019 KoS on simulation modelling is expected to increase the number of Highly sensitised patients (HSP) from 2% to 4% per year. The simulation modelling clearly showed that this improvement will plateau at approximately 4% and there will not any further year-on-year increase. Biologically (due to the limited HLA types in the organ donor pool) and statistically (as evidenced by simulation modelling prior to 2019 KoS introduction) it is implausible that the KoS will significantly decrease or eliminate the problem of long waiters due to HLA sensitisation. Without access to the pre-implementation KoS simulation modelling, the panel may have mistakenly concluded that the new KoS would reduce the need for additional intervention/s to improve outcomes for HSP. With approximately 20% (>1000 patients) of national kidney transplant waiting list consisting of HSP - it is clear that multiple interventions including the revised KoS and agents such as Imlifidase will be key to improve outcomes. These interventions will benefit different patient groups within the HSP population and as such are not mutually compete for the same patient sub-groups.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The assumption that kidneys not used for HSP (following treatment with Imlifidase) could benefit other recipients on the waiting-list with better cost-effectiveness needs re-evaluation. Please consider reviewing the manuscript by Bernadette Li et al Equity–Efficiency Trade-offs Associated

With Alternative Approaches to Deceased Donor Kidney Allocation: A Patient-level Simulation, Transplantation, Apr 2020, Vol 104, 795-803. This clearly establishes a completely Utility skewed allocation model does not provide overall best ICER/cost per QALY return. Unlike other treatments NICE may consider, the cost to the tax payer is comparing costs of on-going dialysis vs cost of Imlifidase enabled transplantation. A non-transplanted patient continues to accrue costs related to dialysis whilst having declining health status as dialysis is inferior to transplantation. Therefore, comparisons has to be between treatment enabled transplantation vs continued dialysis and not against a control group of transplanting an un-sensitised patient who does not require any additional intervention.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The risks associated with prolonged cold ischaemia time (CIT) are over stated and do not take into account likely clinical practise in a small number of expert centres that can implement an Imlifidase enabled pathway. For eg: it is likely the clinical model could be that these specialised centres would only accept offers from high quality (D1 or D2 in the donor risk quartiles) organ offers for patients who require Imlifidase. These organs are more likely to be able to tolerate the prolongation of CIT from an average of 12 hrs to 18 hrs due to the additional time required for post-Imlifidase cross match. Peripheral blood cross match soon after organ offer acceptance will further help to reduce any CIT accumulating even before organ retrieval is complete. Therefore, within expertly designed pathways for this niche group - kidney transplantation can be done within easily acceptable CIT thresholds of <20 hours and organs accepted will be of sufficient quality to not suffer significant harm by the CIT increase of ~6 hours.

The only other alternative for this patient population is to wait for a long time on the national deceased donor list - denying these patients the opportunity to transplantation because of CIT prolongation of ~6hrs or because 'it is too hard' to incorporate Imlifidase in the patient pathway is disproportionate as the alternative risks of no transplantation is only borne by the patient. Selected centres with required expertise can and will come up with patient pathway designs to mitigate CIT risk sufficiently to ensure safe transplantation.

The requirement for a second dose of Imlifidase is only in <10% of reported patients thus far. Therefore, concerns re prolonged CIT in those requiring 2 doses ignores potential benefit in 90% of patients who need only one dose. With nationally agreed careful patient selection, including the antibody thresholds, it is very likely a number of patients could benefit from Imlifidase with very low risk of needing a second dose pre-operatively, ensuring safe transplantation within acceptable CIT thresholds.

The draft recommendation document does not explain why a managed market access solution to enable further evidence gathering (evidence of safe use within NHS without impacting on CIT as well as patient and graft outcomes) has been ruled out. It is vital to point out this patient group

currently do not have any alternative treatment options other than to wait indefinitely, whilst accruing avoidable morbidity with each passing year on dialysis. As discussed above, the 2019 KoS will not result in a compatible transplant for the vast majority of HSP on the kidney transplant waiting list. A negative recommendation and closure of managed market access pathways effectively condemns HSP to continue to suffer status quo despite a possible treatment option. As a minimum, managed market access to allow data gathering to permit evaluation (both cost effectiveness and operational implementation) within the NHS setting is critical before arriving at any conclusion on potential benefits to the NHS.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

HLA sensitisation and related longer wait-times for a kidney transplant disproportionately affects females (pregnancy related sensitisation) and ethnic minorities (either due to blood transfusions or previous organ transplants). Both these groups are more likely to be sensitised to common Caucasian/Anglo-Saxon HLA types making it much harder to receive a transplant. The long waiter list therefore has a larger proportion of female and non-white ethnicity populations (compared to un-sensitised patients). Recommendation to not support Imlifidase use will have a disproportionately worse impact on female and non-white ethnicity long-waiters for a kidney transplant. The current standard of care is to wait on the national transplant list and it is likely this will result in worsening of health status for women and non-white ethnicity patients compared to men and white ethnicity patients.

Name	[redacted] (NHS blood and transplant)
Comments on the ACD:	

3.2: People who are highly sensitised wait longer for a suitable donor kidney than those who are not sensitised

The recent changes to the UK renal organ allocation system (Implemented Sept 2019) were designed to meet some of the challenges faced by highly sensitised patients awaiting transplantation. Historically these patients have waited for a period of time far greater than those patients who are unsensitised or moderately sensitised and were therefore unable to realise the health and experience benefits a transplant would bring. In some cases where patients are very highly sensitised the only option to proceed to transplant prior to changes in the organ allocation system was to perform a HLAi transplant.

The changes to the renal allocation system in 2019 (and the use of the UKNKSS) have had a positive impact upon the chances of highly sensitised patients awaiting transplant, with many highly sensitised patients receiving a

transplant. However, a small number of very highly sensitised patients (cRF 100%) still face significant challenges in terms of access to transplantation. Using the NHSBT ODT kidney reaction frequency calculation tool (Calculators - ODT Clinical - NHS Blood and Transplant) it is possible to determine the number of potential compatible donors from the last 10,000 UK donors. Using such tools, assessment of some highly sensitised patients reveals that none of the last 10,000 donors would be considered compatible. Indicating that without performing a HLAi transplant these patients will remain untransplantable - despite the changes to organ allocation systems and use of the UKNKSS.

A recent publication examines this challenge within the United Network of Organ Sharing (UNOS) within the US.

Schinstock, CA, Smith, BH, Montgomery, RA, et al. Managing highly sensitized renal transplant candidates in the era of kidney paired donation and the new kidney allocation system: Is there still a role for desensitization? Clin Transplant. 2019; 33:e13751. https://doi.org/10.1111/ctr.13751Sincerely,

This paper identifies a finding within the US that patients with a CPRA of >99.9% may still benefit from a desensitisation program.

A similar analysis in the UK would be of benefit – however given that changes in the organ allocation system in the UK came into place less than 6 months prior to the start of the Covid-19 pandemic sufficient data may not be available.

However, use of the kidney reaction frequency tool by individual H&I laboratories indicates that a small group of patients may still require a HLAi to proceed to transplant as compatible donors are not within the UK donors pool.

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

A Single Technology Appraisal

ERG Review of Company's Response to Appraisal Committee Meeting 2

Produced by

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Declared competing interests of the authors

Since the publication of the original ERG report, Siân Griffin provided paid consultancy services to Hansa BioPharma AB. These services involved providing clinical expert advice on patient eligibility criteria for imlifidase, and the potential treatment pathway for imlifidase in the NHS.

Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This TE response is linked to ERG report

Farmer C, Knowles E, Kiff F, Long L, Robinson S, Nikram E, Powell R, Moore J, Griffin S, Hatswell A, Crathorne L, Melendez-Torres G.J. Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease [ID1672]. Peninsula Technology Assessment Group (PenTAG), 2020.

1. INTRODUCTION

At the second committee meeting for this appraisal on 10 February 2022, the NICE committee were unable to recommend imlifidase for routine commissioning due to uncertainties in the evidence base. On 7 April 2022, the company submitted a response to the uncertainties raised by the NICE committee and the Evidence Review Group (ERG). This document provides the ERG's critique of this response.

The company did not provide any new evidence in response to the uncertainties raised by the committee, but provided a written argument of the existing evidence base to each of the points raised by the committee. Finally, the company changed the Patient Access Scheme (PAS) discount for imlifidase from [redacted] to [redacted].

2. ERG RESPONSE TO COMPANY'S WRITTEN SUBMISSION

In this section the ERG provide a response to the evidence presented by the company in response to the ACD. Where relevant we provide a reference to where the ERG has previously appraised evidence submitted by the company at other stages of the appraisal.

2.1. ACD Section 3.1. Renal replacement therapies while waiting for a kidney transplant can have a substantial effect on quality of life

There is agreement between the NICE committee, company and ERG about the detrimental impact of clinical management for chronic kidney disease (CKD) without a transplant. Relevant sections where the ERG has explored different utility sources are the ERG report Section 4.27, and in Section 6 of the ERG response to the updated company submission following AC1. The company suggest that the committee should consider the value that imlifidase may offer in providing greater hope for a transplant to people with CKD; however, the company have not provided evidence or a rationale for why any such benefit would not be captured in utility estimates used in the company and ERG models.

2.2. ACD section 3.3. People who have waited a long time for a transplant may not be well enough to have one by the time a suitable donor is found

The ERG agree that as imlifidase is intended for use with deceased donor transplants only, other desensitisation regimes are typically impractical and therefore not an alternative to imlifidase.

2.3. ACD Section 3.4 Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people

The committee raised concerns that those receiving imlifidase will require an intensive immunosuppression regimen, which is consistent with the trial evidence for imlifidase, and clinical advice to the ERG. The company propose that the consequences of this treatment are preferable to the impact of remaining on clinical management without a kidney transplant; however, no data to support this assertion has been provided. Without a matched comparison for patients treated with imlifidase, it is not possible to draw firm conclusions about the relative impact of each treatment option on quality of life. No quality of life data were collected in the trials of imlifidase, though the company have proposed to collect this as part of their post-authorisation study (PAES).

2.4. ACD Section 3.6. The proposed treatment pathway likely underestimates the impact on cold ischaemic time of the donor kidney

The company notes that long cold ischaemic time (CIT) prior to transplant is unlikely, and may be restricted to the small number of patients who require a second dose of imlifidase. The company also note that adjustment of eligibility criteria and the treatment pathway may reduce the likelihood of a 2nd dose of imlifidase. The ERG have argued these points previously, for example in Section 3.2 of the ERG response to the updated company submission following AC1. The ERG have also noted previously that the 6-hour turnaround time used for crossmatch testing in the treatment pathway presented by the ERG was intended to represent the upper bounds of what may be expected. However, the ERG maintain that these estimates are nevertheless plausible within the proposed treatment pathway described by the company in their submission, and were based on input from clinical advisors. The ERG further note that clinical advisors within the NICE committee felt the timeline proposed by the ERG could have been further extended to account for the potential pressures within the health service that may further extend CIT. While the eligibility characteristics for imlifidase and the proposed treatment pathway may be altered with further experience of its use in the NHS, without firm data on this process the ERG is unable to revise its appraisal of the risk of long CIT and the potential impact this may have on patient outcomes following transplant.

The company further note that a kidney may still be used following a CIT of 24 hours, and does not become unusable as stated in the ACD. The ERG agree with this, although note that clinical advice to the ERG was that a CIT above 24 hours was considered to have more serious repercussions for transplant outcomes. The ERG expects that clinicians may consider the length of CIT and the potential consequences of this when deciding whether to proceed with a transplant.

The company do not consider that the requirement for a 2nd dose of imlifidase should prevent patients from receiving a transplant, due to the impact of CIT on transplant outcomes. They note that no kidneys were wasted within the trials of imlifidase, and that a multidisciplinary team overseeing the use of imlifidase in the NHS can weigh the potential risks and benefits on a case by case basis. The company also note that measures may be implemented to reduce the risk of wastage, for example by scheduling a back-up patient. The ERG agree with the points raised by the company, though reiterate that the short follow-up duration of the trials of imlifidase mean it is not possible to determine the true impact of longer CIT on transplant outcomes. The ERG therefore still consider it plausible that those with longer CIT, for example due to the need for a

2nd dose, may experience poorer transplant outcomes, and that this issue should be considered by the NICE committee when interpreting the clinical evidence.

Finally, the company present data showing variation in CIT between trial sites in the US and the EU (Sweden), suggesting that CIT in the UK may be closer to the CIT in the EU sites due to the small geographical area. Based on the data presented, it was not possible to determine whether variation between sites was due to the proximity of kidneys to the recipient, or due to other factors such as differences in the healthcare system or treatment pathway. Transport times for each site were not presented, and therefore it was not possible to compare these with the potential transport times expected in the UK. Clinical advice to the ERG and NICE committee supports proposals by the company that treatment with imlifidase would be expected to be delivered in a small number of specialist centres in the UK, and therefore some transport time will be needed to transport kidneys and recipients to the closest centre. Despite the new data provided by the company, the ERG still consider long CIT to be plausible in a small number of patients, based on information provided by the company and clinical advisors about the likely time needed to conduct required testing and infusions.

2.5. ACD Section 3.7. Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised

The ERG have previously discussed this issue in Sections 2.4, 3.1 – 3.2, 4.1 – 4.2, and 6.2– 6.3 of the ERG report.

2.6. ACD Section 3.8. The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS (cf similar drugs for rare diseases)

The ERG do not consider the company's response—that the trial data are robust and sufficient to grant conditional marketing authorisation for imlifidase—adequate to resolve this issue. Only a very small number of patients provided data at the final 3-year follow-up timepoint, and even where short-term data are robust, this does not resolve the need for longer follow-up. Clinical advice to the ERG is that longer follow-up is needed to determine the longevity of kidney transplants following treatment with imlifidase, and the requirement for further care. The ERG further note that a conditional marketing authorisation is awarded where licensing bodies are unable to award full authorisation due to insufficient evidence. The conditional marketing

authorisation for imlifidase has been given by the European Medincines Agency (EMA) pending further evidence for the longer term effectiveness and safety of imlifidase.

2.7. ACD Section 3.9. Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm (cf likelihood of not receiving a transplant whatsoever)

The ERG have stated previously that the high rate of AMR in people treated with imlifidase is consistent with the rate expected following other desensitisation regimens (e.g. ERG report Section 3.2.4.4). However, the ERG do not consider that the issue raised by the committee has been addressed by the company. This issue relates to the potential for improved outcomes following a compatible transplant as compared to an incompatible transplant following imlifidase, which the ERG still expects to be the case.

2.8. ACD Section 3.11. Data shows that some people for whom imlifidase might be suitable already have access to transplants

The ERG disagree with the company that there is a conflict between statements made in the ACD, since statements acknowledge that some though not all patients eligible for imlifidase may receive a compatible kidney through the kidney offering scheme (KOS). Following amendments to the KOS, highly sensitised patients are now more likely to receive a compatible transplant. However, clinical advice to the ERG is that the full impact of these changes is not yet clear due to the impact of the COVID pandemic on transplants since the changes were implemented. As those who receive a compatible transplant may be expected to have improved transplant outcomes relative to an incompatible transplant following imlifidase, the ERG expects that clinicians and patients will need to consider the relative risks and benefits of using imlifidase versus waiting longer for a match. The ERG considers that changes made by the company to the eligibility criteria for imlifidase, namely for patients to have waited 2 or more years on the waitlist and for patients to be fully appraised of the potential for increased risks, seek to address this issue.

2.9. ACD Section 3.12. Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain

Due to the small sample size of the trials of imlifidase, the changing patient eligibility criteria for imflidase (both during the appraisal and where expected following a positive recommendation for imlifidase), and forthcoming evidence on the impact of changes to the KOS, the ERG

consider that the proportion of patients who receive imlifidase but not a transplant is uncertain. The ERG agree that the transplant rate following imlifidase is very high, though note that small changes in this rate has an impact on the ICER for imlifidase (see Section 6.4 of the ERG report).

2.10. ACD Section 3.18. Specific consideration needs to be given to people who have become highly sensitised through pregnancy

The ERG acknowledge that pregnancy is one of reasons why people may become highly sensitised, though did not identify this as an equality issue during its appraisal.

2.11. ACD Section 3.19. Imlifidase could provide a step-change in treatment but there are challenges/alterations for implementation

The company propose that challenges for implementation should not prevent a recommendation for the treatment, given it represents a step-change in treatment for this condition. The ERG accept that some uncertainties about implementation may be present with innovative treatments, particularly when a new treatment pathway is required. However, the ERG consider the uncertainties for the implementation of imlifidase are relevant to discussion by the committee, given that alterations in implementation are expected to alter the eligibility criteria for imlifidase, and the likely clinical and cost outcomes of the treatment.

2.12. ACD Section 3.20. Managed access agreement is not appropriate

The decision as to whether a managed access agreement would be appropriate is a decision for the relevant teams at NICE and NHS England. The company propose that the forthcoming post-authorisation study for imlifdase (PAES) will deliver evidence that would be useful for committee decision-making. As noted by the ERG in its response to the company's updated evidence submission following AC1 (Sections 3.5 and 7.2), this study may not be sufficient to resolve all uncertainties in the evidence base due to the study design (an observational open-label study), and the anticipation of short and limited follow-up timepoints in a small number of patients. To the ERG's knowledge, the protocol for this study has not yet been finalised, and has not been submitted by the company as part of this appraisal.

2.13. ACD Section 3.13 Graft survival projections from iBox are highly uncertain so a hazard ratio should be applied to account for this

The company recommend in their response that the iBox graft survival extrapolation is a relevant scenario to validate the imlifidase trial data against, and that the imlifidase trial data

should be used to inform graft survival in the model. However, the ERG highlights that in the company's original submission the iBox was the company's preferred source to inform graft survival in the model as they felt it provided the most reasonable projections. The ERG had concerns regarding the generalisability between the imlifidase trial and iBox populations with 60% and 15% of patients receiving a subsequent transplant respectively, however the ERG considered the iBox the best available source to inform graft survival given the immaturity of the trial data. Following ACD1, the committee considered the iBox projection and extrapolation to be too optimistic, particularly at 20 years. The company revised its base case ahead of AC2 to use the imlifidase unlikely to be transplanted population to inform graft survival, which did not address the concerns of the committee as projections were more optimistic in this group compared to the iBox. The ERG did not consider the use of this data to be a reasonable assumption. The ERG opted to use the iBox predictions in the ERG base case with a 0.9 hazard ratio (HR) applied in order to produce less optimistic projections of graft survival over time to align with clinical opinion and the committee consideration that iBox projections alone are too optimistic. A detailed rationale for using the iBox projections over the imlifidase trial data including expert clinical estimates is provided in the Section 4.1.9. of the ERG's response to the updated company submission following AC1.

The company also provide estimates of 5-year and 10-year graft survival estimates in their response from the NHSBT Annual report[1] and Krishnan et al. 2021[2], replicated below in Table 1.

The ERG notes that the NHSBT data[1] are for patients receiving their first kidney transplant only which is not aligned with the trial population where 60% of patients received a subsequent transplant. As clinical opinion indicated that patients receiving a subsequent transplant would be expected to have poorer graft survival than those who are transplant-naïve, the ERG does not consider the NHSBT projections to reasonably reflect the graft survival that would be expected in the patients from the imlifidase trials.

The ERG also notes that 88.1% of patients in the Krishnan study[2] received living donor transplants. As imlifidase would only be eligible for deceased donor transplants and there is evidence to support greater graft survival in living donor transplants, the ERG does not consider the projections from this study to be comparable for the population treated with imlifidase.

Table 1: Graft survival projections

Source	5-year graft survival	10-year graft survival
NHSBT 2007-2009, DCD 3	0.86	0.75
NHSBT 2013-2015, DCD 3	0.86	-
NHSBT 2007-2009, DBD 3	0.85	0.74
NHSBT 2013-2015, DBD3	0.87	-
Krishnan et al, 2021, HLAi cohort8	0.85	0.70
Imlifidase iBox	[redacted]	[redacted]
Imlifidase iBox, HR 0.9	[redacted]	[redacted]
All imlifidase extrapolations	[redacted]	[redacted]
UTT imlifidase extrapolations	[redacted]	[redacted]

As previously highlighted by the ERG, the exponential model used to extrapolate the mlifidase trial data imposes a constant risk of graft failure over time which is inconsistent with the log-cumulative hazard plot and the nature of transplantation where it is known that the risk of failure is greatest in the period immediately following transplant and reducing over time, that is, not constant. Given the scarcity of data available, it is unlikely that any parametric extrapolation would be able to produce a reasonable long-term estimate. Therefore, clinical opinion is required to provide plausible projections in the long-term.

Overall, the ERG's stance regarding graft survival remains unchanged and uses the iBox Weibull extrapolation with a 0.9 hazard ratio (HR) applied in the ERG base case. The company's approach to use the "Unlikely to be transplanted" data to inform graft survival does not address the committee's concerns that the iBox estimates are too optimistic. Further to this, the 5-year and 10-year estimates from the NHSBT annual report[1] and Krishnan et al.[2] are not in an aligned population, therefore the ERG do not consider these estimates reflective of the patients in the imlifidase trials. The 0.9 HR applied is an arbitrary value thus carries uncertainty however, due to a lack of long-term data in the appropriate population, provides the committee with less optimistic estimates of graft survival for decision making, aligned with the committee's previous concerns.

3. UPDATED COMPANY'S COST-EFFECTIVENESS RESULTS

3.1. Company's base case results

There have been several company and ERG base cases throughout this appraisal which are documented through the ERG report and responses. This document discusses the base cases considered at ACD2 and the revised base case only. For more information on previous base case assumptions and results, please see the the ERG report and response documents.

Results of the company's base case analysis are presented as an ICER for imlifidase with transplant compared to SoC. Total and incremental costs, QALYs and life years (LYs) are presented for the company's ACD2 base case in the company's response to ERG questions prior to ACD2 and the company's response to ACD2 for the revised base case, replicated in Table 2. [redacted] patient access schemes (PASs) of [redacted] and [redacted] were applied to the acquisition cost of imlifidase in the ACD2 and revised company base cases, respectively. The ERG notes that prior to ACD2 the company requested a change to their PAS discount from [redacted] to [redacted]; however, the slides for ACD2 report the results corresponding with the [redacted] discount therefore, the ERG has aligned with this approach for consistency.

Table 2: Original and revised company base case deterministic results

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
ACD2 company base case (deterministic) – [redacted] PAS discount							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case (deterministic) – [redacted] PAS discount							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; QALY, quality adjusted life year; SoC, standard of care.

The company reported a revised base case ICER of [redacted] for imlifidase versus SoC, based on incremental costs of [redacted] and a QALY gain of [redacted]. The revised base case analysis projected [redacted] discounted LYs for patients treated with imlifidase who go on to receive a transplant, of which [redacted] were gained in the 'functioning graft' health state.

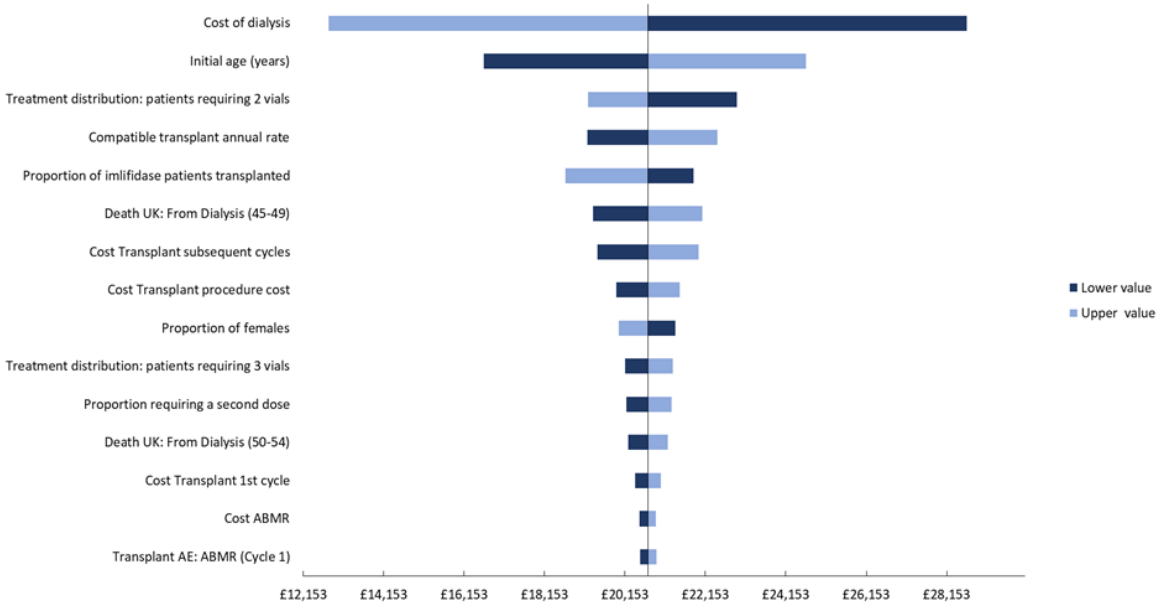
3.2. Company's sensitivity analysis

The company provided one-way sensitivity analysis (OWSA), probabilistic sensitivity analysis (PSA) and scenario analysis results as part of their response to ACD2, discussed in turn below.

3.2.1. Company's one-way sensitivity analysis

A tornado plot was used to present the OWSA results (company response to ACD2, presented in Figure 1), with the ICER as the outcome of interest. The plot showed the results were most sensitive to the cost of dialysis, initial age, proportion of patients requiring 2 vials of imlifidase for a single dose (based on patient weight), the proportion of imlifidase patients transplanted and the compatible transplant annual rate (applied in the SoC arm). None of the parameter changes resulted in an ICER over £30,000. As the ERG has previously noted, the proportion of patients requiring 1, 2 and 3 vials should not have been included in the OWSA as these are not independent parameters.

Figure 1: Company's OWSA Tornado plot – [redacted]



Abbreviations: ABMR, antibody-mediated rejection

3.2.2. Company's probabilistic sensitivity analysis

In the company's response to ERG questions, the company provided results of a probabilistic sensitivity analysis (PSA) to explore the impact of parameter uncertainty, based on each model parameters' respective distribution. Though not stated, the ERG anticipates that 10,000 iterations were used within the PSA. The ERG has repeatedly noted throughout the appriasal

process that graft survival is not included in the PSA, meaning the results underestimate the uncertainty in the decision problem. The ERG notes that graft survival is still not included in the company's revised PSA.

The PSA results were summarised in the company response to ACD2 in a results table (recreated here in Table 3), cost-effectiveness plane and cost-effectiveness aceptability curve (CEAC).

The company's probabilistic base case ICER is similar to the deterministic result ([redacted]), though the results do not represent the true full uncertainty in the decision problem as graft survival was not included in the PSA.

Table 3: Revised company mean PSA results (company presented, ERG corrected) – [redacted]

Arm	Totals		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Company probabilistic base case					
Imlifidase	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year.

Notes:

* ERG re-run of the PSA using the company's base case assumptions

At a willingness-to-pay threshold of £30,000 per QALY gained, the probability of imlifidase being cost-effective versus SoC was 80.6%. However, as previously mentioned, these results do not account for any uncertainty around graft survival extrapolation.

3.2.3. Company's scenario analysis

The company provided eight scenario analyses in response to ACD2. Seven of the scenarios have previously been presented by the company with an additional scenario exploring Krishnan et al., estimates to inform graft survival.

All original scenarios resulted in an increase to the ICER, with all but two scenarios remaining below £30,000. These increases over the threshold occur when a 10-year time horizon is assumed and when changing the overall survival with a functioning graft data source from 'all imlifidase' to the more-closely aligned target population 'unlikely to be transplanted', with ICERs of [redacted] and [redacted], respectively. The new scenario using Krishnan et al.[2] data to inform

graft survival resulted in a decrease in the ICER to [redacted]. However, as discussed in Section 2.13, the ERG notes that the population in Krishnan et al. does not align well with those eligible for imlifidase as the subjects in the study primarily received living donor transplants (88.1%), which are are associated with improved outcomes compared to deceased donor transplants where imlifidase would be administered.

The scenario analyses presented were limited in number, with none exploring the impact of model selection on survival extrapolation, or the impact of an alternative dialysis overall survival approach. The scenario analysis results did however, highlight that nearly all alternative assumptions to the company's base case result in an increased ICER and illustrate the influence of the data used to extrapolate overall survival with a functioning graft upon the cost-effectiveness results.

4. UPDATED ERG COST-EFFECTIVENESS RESULTS

In the company's revised submission, several of the ERG's preferred assumptions were accepted.

4.1. ERG base case results

The ERG determined a set of preferred settings and assumptions that were believed to represent a more plausible estimate of the cost-effectiveness of imlifidase. However, the ERG emphasises that several preferred assumptions such as graft survival estimates and the proportion of imlifidase patients who are likely to receive a transplant without imlifidase remain uncertain.

The ERG's preferred model settings and assumptions are summarised in Table 4. The previous preferred ERG assumptions of allowing 5% of SoC patients to receive no dialysis, increasing the number of crossmatch tests following imlifidase to 2.42 and allowing patients in the SoC arm to receive a transplant in cycle 0 (to align with imlifidase) have now been accepted by the company. Therefore, the only remaining discrepancy between the company and ERG's base cases is the efficacy data used to inform graft survival in the model.

Table 4: ERG's preferred model assumptions – [redacted]

Preferred assumption	Section in ERG response to company's revised submission	Individual change to corrected ICER £/QALY	Cumulative ICER £/QALY
Company base case	*Section 3.1*	[redacted]	[redacted]
Use iBox predictions to inform graft survival with a 0.9 HR	*Section 2.13 & 4.1*	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year; SoC, standard of care.

A comparison of the revised company's base case analysis and the revised ERG's preferred analysis results are presented in Table 5. The equivalent results of PSA using the ERG preferred assumptions are also provided.

Table 5: Comparison of company and ERG results – [redacted]

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Company base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company probabilistic base case							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base case (probabilistic)							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Notes: It was not possible to obtain PSA LY results from the cost-effectiveness model.

4.2. ERG sensitivity analyses

A comparison of the company's and ERG's scenario analyses using the ERG's preferred assumptions versus the company's base case is provided in Table 6. The majority of changes result in an increase to both the company's and ERG's base case results.

OS with a functioning graft remains a key area of uncertainty in the model with a lack of long-term data to inform the outcome. The base case ICERs when changing from the "All imlifidase" to the "Unlikely to be transplanted" data to inform the endpoint are [redacted] (company) and [redacted] (ERG). The "All imlifidase" data is utilised in the ERG base case in the absence of better data; however, the ERG considers neither data source to be optimal for informing the outcome and that both data sources are fairly equal in their capability to estimate survival with a functioning graft. Further to this, the ERG notes that there is no strong rationale for selecting this data over the "Unlikely to be transplanted" population other than increased patient numbers in the "All imlifidase" population. The "Unlikely to be transplanted" data are more aligned to the eligible population for imlifidase and could reasonably be argued as the more appropriate data source.

Table 6: Comparison of company and ERG scenario analysis results – [redacted]

Scenario	ICER (£/QALY)	
	Company	ERG
Base case	[redacted]	[redacted]
Company scenario analyses		
Time horizon – 10 years	[redacted]	[redacted]
Time horizon – 20 years	[redacted]	[redacted]
Graft loss extrapolation – iBox*	[redacted]	[redacted]
Graft loss extrapolation – All imlifidase patients	[redacted]	[redacted]
Graft loss extrapolation – Krishnan et al.[2]	[redacted]	[redacted]
OS with a functioning graft – 'Unlikely to be transplanted' patients	[redacted]	[redacted]
No caregiver disutility	[redacted]	[redacted]
Caregiver disutility source – Nagawasa *et al* (2018)[3]	[redacted]	[redacted]
ERG scenario analyses		
Utility source – Cooper *et al* (2020)[4]	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 94.4%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 90%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 99%	[redacted]	[redacted]
SoC annual compatible transplant rate – 5%	[redacted]	[redacted]
SoC annual compatible transplant rate – 10%	[redacted]	[redacted]
SoC annual compatible transplant rate – 15%	[redacted]	[redacted]
SoC proportion on 'no dialysis' – 0%	[redacted]	[redacted]
SoC proportion on 'no dialysis' – 10%	[redacted]	[redacted]
Number of crossmatch tests following a full dose of imlifidase - 1	[redacted]	[redacted]
Number of crossmatch tests following a full dose of imlifidase – 5	[redacted]	[redacted]
Number of DSA tests - 1	[redacted]	[redacted]
Number of DSA tests - 6	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.80	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.85	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.95	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Apply alternative transplant cost - £21,000	[redacted]	[redacted]
Change OS dialysis source – ERA-EDTA	[redacted]	[redacted]

Scenario	ICER (£/QALY)	
	Company	ERG
Apply HR to “Unlikely to be transplanted” graft survival – 0.9 **	[redacted]	[redacted]
Apply HR to “Unlikely to be transplanted” graft survival – 0.98 **	[redacted]	[redacted]

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

Note: * iBox data to inform graft survival is applied with no HR in this scenario.

** “Unlikely to be transplanted” data is used to inform graft survival in these scenarios.

5. ERG OVERVIEW OF STAKEHOLDER SUBMISSIONS

Following the committee decision not to recommend imlifidase for routine commissioning, the NICE committee sought submissions from key stakeholders. Submissions were received from The British Transplant Society (BTS), the NHS England and Improvement Clinical Reference Group (CRG) on Transplantation issues, and from clinical experts who submitted individual responses as members of the public (including two stakeholders from NHS blood and transplant, a stakeholder from Belfast Trust HSC, a stakeholder from University Hospitals Coventry and Warwickshire, and a stakeholder from North Bristol NHS Trust).

5.1. The proposed treatment pathway likely underestimates the impact of cold ischaemic time of the donor kidney

The representatives from the BTS and NHSE did not consider imlifidase to have an unreasonable effect on the cold ischaemic time (CIT) of the kidney, particularly for those receiving one dose of imlifidase. In these patients BTS considered the CIT of the kidney after arrival at the transplanting centre (i.e. not including transport time) to be <12 hours. While the addition of transport time and, where required, time to infuse a 2nd dose of imlifidase and perform additional crossmatch test(s) was not mentioned explicitly; the stakeholder cited evidence from a UK study suggesting that a CIT up to 24 hours is not associated with adverse outcomes.[5] This point was also made by the stakeholder from NHSE, accompanied by another citation from the same author.[6] In addition. Stakeholders including those from clinicians submitting responses as members of the public suggested that a number of steps could be taken to reduce CIT, including careful patient selection, and transport of a blood sample prior to extraction of the kidney from a deceased after brain death donor. It was also noted that there is an existing system to re-allocate kidneys where needed and thus reduce the risk of wastage. .

5.2. Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are non-sensitized.

The representatives from BTS, NHSE, Belfast, Bristol and Warwick did not agree that the decision to recommend for imlifidase should consider the opportunity cost for the kidney in other recipients who may have improved outcomes with the same kidney. The submission from BTS notes that poorer transplant outcomes may be expected according to prognostic markers in the non-sensitised population, but that the transplant system does not discriminate against people

with these markers. The submission also noted that in the current system, imlifidase may instead improve the inequity of access to kidneys for sensitised patients.

5.3. Data shows that some people for whom Imlifidase might be suitable already have access to transplants

The representative(s) from BTS considered the estimate of 31.4% to be a reasonable estimate of the target population for imlifidase who would receive a transplant while on the waiting list without the use of imlifidase. They considered that the use of a 2-year waiting rule for imlifidase was a reasonable approach to give some patients the opportunity to receive a compatible transplant. However, the representative from NHSE suggested patients should initially remain on the waiting list for 4 or 5 years, at least until further data about the way changes to the kidney offering scheme will have affected the likelihood of a highly sensitised patient receiving a kidney. It was noted that after 4-5 years however, patients on dialysis are at a higher risk of cardiovascular morbidity and mortality. This concern was also raised by the stakeholder for Warwick, who cited evidence of poorer outcomes in those on dialysis for longer, which may mean they are no longer eligible to receive a transplant. Several stakeholders noted that changes to the kidney offering scheme to increase the likelihood that sensitised patients receive a transplant will nevertheless leave some sensitised patients without a transplant.

5.4. Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm

The representative(s) from BTS suggested that the eligibility criteria for imlifidase may benefit from being adapted to exclude patients with extreme levels of DSA, which may reduce or eradicate the failure of imlifidase to achieve a crossmatch conversion. In addition, it was proposed that imlifidase be reserved for “acceptable but incompatible HLA specificities”, thus avoiding transplants with strong positive CDC crossmatch. They propose that this would reduce the incidence of AMR in those transplanted, and may lead to improved long-term outcomes. The stakeholder from NHSE noted that those who do experience AMR following the transplant may nevertheless experience many years of transplant survival and improved quality of life relative to dialysis, even if kidney function is reduced. Stakeholders noted that a 40% rate of AMR anfd poorer graft survival would be expected following any incompatible transplant, including those facilitated by other desensitisation strategies

5.5. Not everyone who has Imlifidase treatment goes on to have a kidney transplant, but the exact proportion is uncertain

The stakeholder from BTS proposed that the adjustment of eligibility criteria for imlifidase may alter this proportion. A stakeholder from NHSBT noted that there is variation in the likelihood of transplant within those with CRF varying by one decimal place, and therefore more precise estimates of CRF should be used.

5.6. The number of cross match tests will likely be higher than 1 and should be included in the economic model.

The stakeholder from BTS proposed that the adjustment of eligibility criteria for imlifidase may alter the number of crossmatch tests required. Representatives from both BTS and NHSE noted that the cost of crossmatch tests are low, and may therefore have limited impact on the costs of treatment with imlifidase.

5.7. Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people

Stakeholders from Belfast and Warwick note that a higher immunosuppression regimen will always be required for highly sensitised patients receiving an incompatible transplant.

5.8. The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS

Several stakeholders recognise the limited data for imlifidase and note that further data will be useful; however, they consider that potential merits of imlifidase are already evident. It was noted that survival following other desensitisation treatments has been shown to be improved compared to treatment with dialysis alone. The stakeholder from Belfast further notes that data at 3-year follow-up would be sufficient to pick up rates of early graft loss from AMR.

5.9. Imlifidase could provide a step-change in treatment but there are challenges in implementation.

Several stakeholders recognised imlifidase as a step change in treatment for highly sensitised patients. The stakeholder from BTS suggested that the introduction of imlifidase in the UK should be a careful and nationally coordinated process, drawing upon the experience and data collection capacity of NHSBT. The stakeholder from Warwick proposed that treatment with imlifidase should initially be restricted to two specialist centres, and expanded as required.

5.10. Other comments

A stakeholder from NHSBT and from Warwick proposed that the title of this NICE appraisal is misleading, as imlifidase only aims to prevent hyperacute rejection caused be pre-existing donor-specific antibodies. Other types of rejection, such as acute and chronic AMR and ACR should be unaffected.

A stakeholder considered that the company should have submitted evidence on outcomes, including rejection rates, from populations receiving other desensitisation therapies (e.g. plasma exchange, immunoadsorption, double filtration plasmapheresis).

A stakeholder from NHSBT noted that it's misleading to state that "a small number of people could wait up to 7 years", as there may be patients waiting longer than 7 years and these patients then accumulate on the waiting list.

Two stakeholders considered that imlifidase could reduce inequity for those with sensitivity due to pregnancy.

Two stakeholders considered that imlifidase should be restricted to the most sensitised patients.

A stakeholder from Belfast proposed that the costs of imlifidase would be improved if it was being used in living donor transplants.

A stakeholder from Warwick suggested that it was not uncommon for people to receive a transplant without first receiving dialysis.

A stakeholder proposed that estimates for graft survival using iBox may not be reliable due to the complexity of antibody incompatible transplantation.

A stakeholder from Bristol requested further clarification on why a managed access agreement was not considered appropriate.

6. REFERENCES

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Additional scenario analyses for 2nd dose population carried out by ERG during pre-meeting

Background

- The requested scenario was to allow only 1 dose of imlifidase per patient, therefore it is assumed that 0% of patients received a 2nd dose and that those patients who required a second dose in the trials ([redacted] patients from the "All imlifidase" population) remain on dialysis treatment instead (i.e., do not receive a transplant)
- Currently in the base case, the proportion of patients assumed to receive imlifidase but no subsequent transplant is 2 out of 54 patients (n=54 referring to all patients who received imlifidase in the trials)
- There was an additional patient who did not achieve a negative FACS crossmatch but received a transplant anyway. Previously the ERG have provided a scenario analysis where this patient is also assumed not to receive a transplant after imlifidase due to the patient not achieving the negative crossmatch

Scenario 1

- Proportion of patients receiving a second dose set to 0%
- Proportion of patients receiving a transplant after imlifidase set to [redacted]
    - Calculation: (Proportion of patients receiving a transplant) * (proportion of patients requiring 1 dose of imlifidase only) = [redacted]

Scenario 2

- Proportion of patients receiving a second dose set to 0%
- Proportion of patients receiving a transplant after imlifidase set to [redacted]
    - Calculation: (Proportion of patients receiving a transplant) * (proportion of patients with negative crossmatch) * (proportion of patients requiring 1 dose of imlifidase only) = [redacted]

Limitations:

- The company have not provided the proportion of patients who needed a 2nd dose of imlifidase for the entire population (n=54) therefore these scenario analyses can only be run using the proportion provided for the "All imlifidase" population. There were possibly more 2nd doses required (meaning a decrease in the proportion who would receive a transplant if only 1 dose is allowed) but the ERG does not have access to that information. Equally, the number of patients may not change in which case only [redacted] of 54 patients would require a 2nd dose and the proportion of patients receiving a transplant would increase.

Results:

	Base case	Scenario 1	Scenario 2	Incremental change Scenario 1	Incremental change Scenario 2
Company	£20,725	£21,551	£22,686	+£826	+£1,961
ERG	£28,014	£28,965	£30,266	+£951	+£2,252

Hansa deterministic results using the ERG preferred model assumptions (graft survival based on the iBox data with a hazard ratio of 0.9, patient survival based on the UT population): [redacted]

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

Hansa deterministic base case results (using graft survival based on the 3 years data extrapolation and patient survival based on the All imlifidase): [redacted]

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

Hansa base case probabilistic results (3-year data extrapolation, All imlifidase patient survival): [redacted]

	Costs (£)			QALY			ICER (£/QALY)
	Imlifidase and transplant	**Dialysis**	**Incremental**	**Imlifidase and transplant**	**Dialysis**	**Incremental**	
Reference case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

PSA scatter plot (3-year data extrapolation, All imlifidase patient survival): [redacted]

[redacted]

PSA, probabilistic sensitivity analysis.; CE cost-effectiveness

Cost-effectiveness acceptability curve of imlifidase (3-year data extrapolation, All imlifidase patient survival): [redacted]

[redacted]

WTP, willingness to pay.

Results of the one-way sensitivity analysis (3-year data extrapolation, All imlifidase patient survival): [redacted]

[redacted]

AMBR, antibody-mediated rejection.

Results of the scenario analyses (3-year data extrapolation, All imlifidase patient survival): [redacted]

	Δ Costs (discounted), £	Δ QALY (discounted),	ICER, £	Difference from baseline, %
Reference Case	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Time horizon, 10 years	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Time horizon, 20 years	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Graft loss extrapolations, iBox	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Graft loss extrapolations, All	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Graft loss extrapolations, Krishnan et al. 2021	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Survival extrapolations, UT	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: No caregiver disutility	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Caregiver disutility (Nagawasa et al. 2018)	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; UT, unlikely to be transplanted

Base case probabilistic results (iBox, UT patient survival): [redacted]

	Costs (£)			QALY			ICER (£/QALY)
	Imlifidase and transplant	**Dialysis**	**Incremental**	**Imlifidase and transplant**	**Dialysis**	**Incremental**	
Reference case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

PSA scatter plot (iBox, UT patient survival): [redacted]

[redacted]

PSA, probabilistic sensitivity analysis.; CE cost-effectiveness

Cost-effectiveness acceptability curve of imlifidase (ibox, UT patient survival): [redacted]

[redacted]

WTP, willingness to pay.

Results of the one-way sensitivity analysis (iBox, UT patient survival): [redacted]

[redacted]

AMBR, antibody-mediated rejection.

Results of the scenario analyses (iBox, UT patient survival): [redacted]

	Δ Costs (discounted), £	Δ QALY (discounted),	ICER, £	Difference from baseline, %

Reference Case	[redacted]	[redacted]	[redacted]	
Scenario 1: Time horizon, 10 years	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Time horizon, 20 years	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Graft loss extrapolations, UT	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Graft loss extrapolations, All	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Graft loss extrapolations, Krishnan et al. 2021	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Survival extrapolations, All	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: No caregiver disutility	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: Caregiver disutility (Nagawasa et al. 2018)	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; UT, unlikely to be transplanted

Company preferred model assumptions (Graft survival – UTT population, OS with functioning graft – All imlifidase population)

Base case

Hansa deterministic base case results (using graft survival based on the 3 years data extrapolation and patient survival based on the All imlifidase): [redacted]

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

Probabilistic sensitivity analysis

Note: Uncertainty related to graft survival is still not included in the PSA.

The PSA 95% CI results were calculated incorrectly by the company. Incremental values should be calculated using the totals reported, not by taking the 2.5% and 97.5% percentiles of all iterations of the incremental PSA results.

For example, the company reported the incremental costs and QALYs as [redacted] and [redacted] for the company base case, lower 95% CI, resulting in a Dominant ICER (fewer costs, greater QALYs). However, the total costs were greater for imlifidase vs. SOC ([redacted] vs. [redacted]), and the incremental value should have been calculated using these totals, resulting in a cost increase of [redacted] associated with imlifidase versus SoC. The correct incremental QALYs are obtained by subtracting the total QALYs for SoC from the total QALYs for imlifidase ([redacted] – [redacted]), resulting in an incremental QALY gain of [redacted]. The resultant ICER then changes from Dominant, to [redacted] when corrected. The same calculation error was found for the PSA upper 95% CI results.

The deterministic and probabilistic mean results presented were correct.

Hansa base case probabilistic results (3-year data extrapolation, All imlifidase patient survival): [redacted]

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Deterministic							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Probabilistic							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic Lower 95% CI							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic Lower 95% CI							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

PSA scatter plot (3-year data extrapolation, All imlifidase patient survival): [redacted]

[redacted]

PSA, probabilistic sensitivity analysis.; CE cost-effectiveness

Cost-effectiveness acceptability curve of imlifidase (3-year data extrapolation, All imlifidase patient survival): [redacted]

[redacted]

The probability of being cost-effective at £30,000 is [redacted]

The probability of being cost-effective at £20,000 is [redacted]

One-way sensitivity analysis

Results of the one-way sensitivity analysis (3-year data extrapolation, All imlifidase patient survival): [redacted]

[redacted]

AMBR, antibody-mediated rejection.

Results of the one-way sensitivity analysis (iBox, UT patient survival): [redacted]

Parameter	ICER (£/QALY)		
	Company	ERG	Variation
Cost of dialysis	[redacted]	[redacted]	[redacted]
Initial age (years)	[redacted]	[redacted]	[redacted]
Death UK: From Dialysis (45-49)	[redacted]	[redacted]	[redacted]
Treatment distribution: patients requiring 2 vials	[redacted]	[redacted]	[redacted]
Compatible transplant annual rate	[redacted]	[redacted]	[redacted]
Proportion of imlifidase patients transplanted	[redacted]	[redacted]	[redacted]
Cost Transplant subsequent cycles	[redacted]	[redacted]	[redacted]
Proportion of females	[redacted]	[redacted]	[redacted]
Cost Transplant procedure cost	[redacted]	[redacted]	[redacted]
Death UK: From Dialysis (50-54)	[redacted]	[redacted]	[redacted]
Treatment distribution: patients requiring 3 vials	[redacted]	[redacted]	[redacted]
Proportion requiring a second dose	[redacted]	[redacted]	[redacted]
Cost Transplant 1st cycle	[redacted]	[redacted]	[redacted]
Cost ABMR	[redacted]	[redacted]	[redacted]
Transplant AE: ABMR (Cycle 1)	[redacted]	[redacted]	[redacted]

ERG preferred model assumptions (Graft survival – iBox with 0.9 HR, OS with functioning graft – UTT population)

Base case

Hansa deterministic results using the ERG preferred model assumptions (graft survival based on the iBox data with a hazard ratio of 0.9, patient survival based on the UT population): [redacted]

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

Probabilistic sensitivity analysis

Note: Uncertainty related to graft survival is still not included in the PSA.

The PSA 95% CI results were calculated incorrectly by the company. Incremental values should be calculated using the totals reported, not by taking the 2.5% and 97.5% percentiles of all iterations of the incremental PSA results.

For example, the company reported the incremental costs and QALYs as [redacted] and [redacted] for the company base case, lower 95% CI, resulting in what the company have defined as a [redacted] ICER (fewer costs, greater QALYs) where in actuality this ICER is in the south-west quadrant (fewer costs, fewer QALYs). However, the total costs were greater for imlifidase vs. SOC ([redacted] vs. [redacted]), and the incremental value should have been calculated using these totals, resulting in a cost increase of [redacted] associated with imlifidase versus SoC. The correct incremental QALYs are obtained by subtracting the total QALYs for SoC from the total QALYs for imlifidase [redacted]), resulting in an incremental QALY loss of [redacted]. The resultant ICER then changes from [redacted], to [redacted] by SoC when corrected. The same calculation error was found for the PSA upper 95% CI results.

The deterministic and probabilistic mean results presented were correct.

Base case probabilistic results (iBox, UT patient survival): [redacted]

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Deterministic							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic							

Arm	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic Lower 95% CI							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic Upper 95% CI							
Imlifidase	[redacted]	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

PSA scatter plot (iBox, UT patient survival): [redacted]

[redacted]

PSA, probabilistic sensitivity analysis.; CE cost-effectiveness

Cost-effectiveness acceptability curve of imlifidase (ibox, UT patient survival): [redacted]

[redacted]

WTP, willingness to pay.

The probability of being cost-effective at £30,000 is [redacted]

The probability of being cost-effective at £20,000 is [redacted]

One-way sensitivity analysis

Results of the one-way sensitivity analysis (iBox, UT patient survival): [redacted]

AMBR, antibody-mediated rejection.

Results of the one-way sensitivity analysis (iBox, UT patient survival): [redacted]

Parameter	ICER (£/QALY)		
	Company	ERG	Variation
Cost of dialysis	[redacted]	[redacted]	[redacted]
Initial age (years)	[redacted]	[redacted]	[redacted]
Treatment distribution: patients requiring 2 vials	[redacted]	[redacted]	[redacted]
Compatible transplant annual rate	[redacted]	[redacted]	[redacted]
Proportion of imlifidase patients transplanted	[redacted]	[redacted]	[redacted]
Cost Transplant subsequent cycles	[redacted]	[redacted]	[redacted]
Cost Transplant procedure cost	[redacted]	[redacted]	[redacted]
Death UK: From Dialysis (45-49)	[redacted]	[redacted]	[redacted]
Treatment distribution: patients requiring 3 vials	[redacted]	[redacted]	[redacted]
Proportion requiring a second dose	[redacted]	[redacted]	[redacted]
Proportion of females	[redacted]	[redacted]	[redacted]
Cost Transplant 1st cycle	[redacted]	[redacted]	[redacted]
Death UK: From Dialysis (50-54)	[redacted]	[redacted]	[redacted]
Cost ABMR	[redacted]	[redacted]	[redacted]
Transplant AE: ABMR (Cycle 1)	[redacted]	[redacted]	[redacted]

Scenario analysis – Both company and ERG preferred model assumptions

Note: The implementation of Krishnan et al., has not been validated by the ERG as the ERG does not consider the population aligned with the patients who would receive imlifidase in clinical practice (88% of patients in Krishnan received a living donor transplant).

Results of the scenario analyses (iBox, UT patient survival): [redacted]

Scenario	ICER (£/QALY)	
	Company	ERG
Base case	[redacted]	[redacted]
Company scenario analyses		
Time horizon – 10 years	[redacted]	[redacted]
Time horizon – 20 years	[redacted]	[redacted]
Graft loss extrapolation – iBox*	[redacted]	[redacted]
Graft loss extrapolation – 'Unlikely to be transplanted' patients	[redacted]	[redacted]
Graft loss extrapolation – All imlifidase patients	[redacted]	[redacted]
Graft loss extrapolation – Krishnan et al.[2]	[redacted]	[redacted]
OS with a functioning graft – 'Unlikely to be transplanted' patients	[redacted]	[redacted]
OS with a functioning graft – All imlifidase patients	[redacted]	[redacted]
No caregiver disutility	[redacted]	[redacted]
Caregiver disutility source – Nagawasa *et al* (2018)[3]	[redacted]	[redacted]
ERG scenario analyses		
Utility source – Cooper *et al* (2020)[4]	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 94.4%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 90%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a transplant – 99%	[redacted]	[redacted]
SoC annual compatible transplant rate – 5%	[redacted]	[redacted]
SoC annual compatible transplant rate – 10%	[redacted]	[redacted]
SoC annual compatible transplant rate – 15%	[redacted]	[redacted]
SoC proportion on 'no dialysis' – 0%	[redacted]	[redacted]
SoC proportion on 'no dialysis' – 10%	[redacted]	[redacted]
Number of crossmatch tests following a full dose of imlifidase - 1	[redacted]	[redacted]
Number of crossmatch tests following a full dose of imlifidase – 5	[redacted]	[redacted]
Number of DSA tests - 1	[redacted]	[redacted]

Scenario	ICER (£/QALY)	
	Company	ERG
Number of DSA tests - 6	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.80	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.85	[redacted]	[redacted]
Apply HR to iBox graft estimates – 0.95	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Proportion of imlifidase patients to receive a second dose – [redacted]%	[redacted]	[redacted]
Apply alternative transplant cost - £21,000	[redacted]	[redacted]
Change OS dialysis source – ERA-EDTA	[redacted]	[redacted]
Apply HR to “Unlikely to be transplanted” graft survival – 0.9 **	[redacted]	[redacted]
Apply HR to “Unlikely to be transplanted” graft survival – 0.98 **	[redacted]	[redacted]
No second dose allowed (Proportion of imlifidase patients to receive a transplant – 96.3%)	[redacted]	[redacted]
No second dose allowed (Proportion of imlifidase patients to receive a transplant – 94.4%)	[redacted]	[redacted]

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

Note: * iBox data to inform graft survival is applied with no HR in this scenario.

** “Unlikely to be transplanted” data is used to inform graft survival in these scenarios.