NICE National Institute for Health and Care Excellence

For public : Contains redacted data

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

Chair's presentation

2nd appraisal meeting - Committee D

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Company: Hansa Biopharma

ERG: PenTAG

10th February 2022

Abbreviations

- +ve: positive
- -ve: negative
- ACM1: appraisal committee meeting 1
- AMR: antibody-mediated rejection
- CDC: complementary dependent cytotoxicity
- CIT: cold ischaemia time
- CMR: cell mediated rejection
- cPRA: calculated panel-reactive antibody
- cRF: calculated reaction frequency
- DD: deceased donor
- DSA: donor specific antibodies
- eGFR: estimated glomerular filtration rate
- ERG: evidence review group
- FACS: fluorescence-activated cell sorting
- FC: flow cytometry
- FCXM: flow cytometry crossmatch
- FU: follow-up
- HLA: human leukocyte antigen
- HR: hazard ratio
- HR-QoL: health related quality of life
- ICER: incremental cost-effectiveness ratio
- KOS: kidney offering scheme
- KT: Kidney Transplant
- MDT: multidisciplinary team
- MFI: mean fluorescence intensity
- NHSBT: NHS Blood and Transplant
- OS: Overall Survival
- PAES: post-authorisation efficacy and safety
- PAS: patient access scheme
- pt: patient
- SoC: standard of care
- tx: treatment
- WL: waiting list
- XM: crossmatch

Summary of appraisal to date

NICE required further information following ACM1 and additional analyses to be completed. Therefore, NICE paused this appraisal pending further work

Following ACM1 NICE requested additional analyses from the company.

Why committee requested further analyses

- The population who would be considered for imlifidase in the NHS was unclear due to changes to the UK Kidney Offering Scheme
- High level of uncertainty relating to long-term clinical effectiveness
- Certain costs not incorporated in the modelling

Analyses requested by the committee

- Better definition of the population in the NHS for whom imlifidase might be suitable, and a more clearly defined pathway.
- More information on the iBox prediction model and long-term graft survival with imlifidase.
- Long-term outcomes data with imlifidase.
- Improved reporting of trial evidence

Key issues

Key issues for ACM2	Impact
1: Population	
• Is the company's new proposed population for imlifidase use appropriately defined?	
2: Treatment pathway	
• Is the proposed imlifidase positioning in the treatment pathway appropriate? Are there any issues with the proposed crossmatch testing schedule?	
3: Updated clinical data	
• Does the additional data submitted reduce uncertainty in the analysis?	
4: Company's updated modelling assumptions	
• What are the most appropriate modelling assumptions/sources?	
5: Potential equality issues	
• Are there any equalities issues that need to be addressed?	
6: Scope of the appraisal	
• Should the committee consider the costs and benefits of kidney transplant in those not eligible to have imlifidase?	

 Model driver  Small impact  Unknown impact

Unresolved | Some discussion | Resolved

Condition background

- Chronic kidney disease - kidneys can't remove waste products as well as they should, blood and protein may leak into urine. Higher risk of developing other conditions including cardiovascular disease
- End stage renal disease - kidney function <10% capacity. Many have regular dialysis, to filter waste products from blood
  - **Kidney transplant preferred option**

4,618 adults on UK kidney transplant waiting list (October 2020)

2,283 adult kidney only transplants from deceased donors in the UK in 2019/20

- Some people have immunological barrier to transplantation – they carry antibodies to human leukocyte antigen (HLA), which is known as being 'sensitised'
  - Exposure to tissue with 'foreign' HLAs is most common cause for sensitisation; can occur from transfusion of blood products, pregnancy or previous transplant
  - Desensitisation is removal of antibodies to HLA
- **People with no appropriate living donor and high level of sensitisation can spend 2-3 years on waiting list for deceased donor kidney**, as they have antibodies against almost all donors' HLA (a 'positive crossmatch')
  - **Aim is to have a 'negative crossmatch' result between deceased donor and person waiting for a kidney, to enable transplant and reduce chance of antibody-mediated rejection of kidney**

Key discussion for this meeting is the company's proposed population for which imlifidase should be used

Patient perspectives

Presented at original committee meeting (Kidney Research, UK)
Statement by patient representative - submitted Feb 2022 (Kidney Care, UK)

- Main options for this group are haemodialysis (HD) or peritoneal dialysis. Haemodialysis stressful, repeated 2 or 3 times a week (around 5 hours each time)
- Dialysis very restrictive - tied to home/dialysis centre, fluid and dietary restrictions, difficult to travel/visit friends, or do full time work. Relationship issues, mental health issues. Disadvantages more difficult to manage over time
- Although dialysis maintains life, prognosis is typically poor - can cause bone disease, heart disease, risk of infections, run out of access to suitable vessels for HD. Long-term dialysis can also shorten life expectancy.
- '*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.
- Finding new treatments that allow kidney patients who would reject their organ transplant is vitally important and this explains why imlifidase could be crucial and meaningful in the life of a kidney patient.

Imlifidase (Idefirix, Hansa Biopharma)

Marketing authorisation*	For desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients
Administration	Intravenous infusion, administered at dose of 0.25mg/kg within 24 hours prior to transplantation. Second dose can be administered within 24 hours after first dose to achieve crossmatch conversion
Price and dosing	Proposed list price £135,000 per vial. Simple discount patient access scheme proposed. Almost all people in trials had more than 1 vial, average course of treatment [redacted] based on • [redacted] • [redacted] • [redacted] (proportion requiring >1 dose could be higher in target population)

*Imlifidase granted conditional marketing authorisation with obligations to submit longer term efficacy data on graft survival by December 2023, and also results on 1 year graft survival rates after desensitisation with imlifidase by December 2025

Summary of committee conclusions from ACM 1

Issue	Committee conclusion	Addressed in responses?
Treatment pathway position, and population	Pathway position and target population of imlifidase is unclear. The treatment pathway should be confirmed and the target population defined	Yes, population and pathway updated.
An intensive immunosuppression regimen is needed for some people	Some people who had imlifidase in trials also had a more intensive regimen of immunosuppression drugs after transplant than is currently used in the NHS for transplants without imlifidase	Company cite clinical advice stating no treatment changes needed
Opportunity cost and equality issues needs to be considered	Imlifidase's value should be based on population benefits and costs. Recommending imlifidase can only be because fairness and equality claims of highly sensitised people outweigh additional costs and loss of benefits to people not highly sensitised	No. Outcomes for the wider transplant population are not explored
Clinical evidence for imlifidase may not be generalisable to NHS practice	National or local transplant protocols have a considerable effect on treatment pathways. Further evidence on pathway position and target population would be useful to determine if trial results are applicable to the NHS	Population and pathway updated. However only XX patients from trials meet criteria

Summary of committee conclusions (2)

Issue	Committee conclusion	Addressed in responses?
Outcomes data below reporting standards for a NICE technology appraisal	The company's clinical evidence was poorly reported, with missing data that would have allowed for full validation. However, the committee acknowledged that the company had provided all the data it had available, but agreed with the ERG that data could have been provided in a more meaningful way.	Company resubmitted data, however infection rate data still not provided
Some people for whom imlifidase might be suitable already have access to transplants	Best available evidence suggests 31.44% in the comparator arm get a transplant without imlifidase. Input from appropriate stakeholders may be needed to better define the population for imlifidase. The refined population may have a lower likelihood of transplant.	Yes, population updated and matched transplant rate included from NHSBT
Not everyone who has imlifidase treatment goes on to have a kidney transplant	The ERG included 2 out of 54 (3.7%) people in the clinical trial who stopped imlifidase before transplant in their model. The ERG also modelled a scenario where 1 patient who partially met criteria did not receive a transplant. Both the ERG's base case and scenario were considered plausible	Yes, proportion receiving transplant in company base case updated to 96.3%

Summary of committee conclusions (3)

Issue	Committee conclusion	Addressed in responses?
Method predicting graft survival after imlifidase could not be examined, and results are uncertain	Graft survival was predicted using iBox. The weight of factors used in iBox were unable to be examined and the population is different to this appraisal population. 20 year graft survival for highly sensitised population was higher than the general transplant population in iBox, which was deemed implausible without evidence. If graft survival after imlifidase was worse than what was modelled, the ICER would increase.	Company now use extrapolation from limited 3 year follow up data. ERG prefers iBox with HR applied.
Company model costs do not incorporate all costs associated with imlifidase	More intensive immunosuppression would be required compared to the NHS population. People may require more than one dose of imlifidase to get a negative crossmatch. Taking these factors into account would increase the ICER.	Partially, XXXX now receive 2nd dose:
Quality-of-life changes from having a transplant with imlifidase are uncertain	The trials for imlifidase did not collect HR-QoL data. HR-QoL was taken from external sources. These sources do not include differences in HR-QoL due to higher levels of antibody-mediated rejection and more intensive immunosuppressive regimens and are therefore uncertain.	No, HR-QoL data was not collected in trials.

Summary of committee preferred assumptions from ACM1

The committee considered several assumptions plausible, based on the previous company proposed population

Scenario	Values/source used
Proportion who had imlifidase and had a subsequent transplant	96.3% and 94.4% (Trial data)
Source of utility data	Li et al. (2017) and Cooper et al. (2020)
Lifetime transplant rate in the comparator arm (based on previous proposed population)	31.44% (NHS Blood and Transplant data)

Cost-effectiveness conclusions:
The true ICER could be higher than that reported in the ERG and company's analysis particularly if any reduction in graft survival that makes a lifetime perspective no longer appropriate.

Summary of clinical and economic evidence

Comparators	**Scope** - Established clinical management without imlifidase: transplant or dialysis **Company** – comparator arm must be receiving dialysis **ERG** - comparator arm should allow for some dialysis use, in line with clinical practice
Clinical trials	4 open label single group trials, phase 2 or phase 1/2, all non-UK: 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04, and 15-HMedIdeS-06. Total = 54 patients. • 25 categorised by company to be 'unlikely to be transplanted,' • XX* meet the new criteria provided by the company; cRF of ≥99%, a matchability score of 10, currently receiving dialysis, and have been on the waiting list for a transplant for at least two years
Main outcome measure	Efficacy on crossmatch conversion (ability to create a negative crossmatch test in people who exhibit donor specific antibodies), kidney function (eGFR)
Model	Partitioned survival model, 3 health states: dialysis, functioning graft, death
Company ICER	**£27,754** (deterministic), **£29,210** (probabilistic; ERG corrected)
ERG ICER	**£37,525** (deterministic), £**38,971** (probabilistic) However the ERG notes that several assumptions are highly uncertain

* Due to lack of evidence both company and ERG model include data from broader patient trial's

Company's response: summary (1)

The company submitted updated analysis based on the request by NICE following ACM1

Key updates in company's submission

Update to the patient eligibility criteria for imlifidase

- cRF ≥99%,
- Matchability Score = 10
- Waiting list time ≥ 2 years
- Suggested patients should be dialysis ≥ 2 years but accept it should not be a requirement

- Clarification of the expected treatment pathway for imlifidase
- Re-submission of clinical effectiveness estimates from the original trial follow-up
- Provision of '3 year' clinical efficacy data from a follow-up trial of imlifidase (Study-14)
- Revised model assumptions
  - Graft survival extrapolation from 3 year clinical efficacy data
  - % in comparator arm receiving transplant (matched NHSBT data)
  - % requiring 2nd dose in intervention arm updated based on new population
- Updated patient access scheme (PAS) discount for imlifidase

Updated scenario analyses include:

- Differing time horizons (10 and 20 years)
- Graft loss extrapolations (iBox, all treated with imlifidase, unlikely to be transplanted)
- No caregiver disutility and caregiver disutility from Nagawasa et al. 2018

Company's response: summary (2)

At factual accuracy check company suggested some changes to their updated analysis

Additional change proposed by company at FAC

Agree with ERG that people not currently receiving dialysis can be included in imlifidase patient population but suggest this represents less than 5% of patients waitlisted (based on clinical feedback showing)

- 40-50% are waitlisted pre-emptively, However, but unusual for those not on dialysis to stay on waiting list for considerably longer than 6 months.
- Approx 3% of all adult Deceased Donor (DD) transplantations are pre-emptive (take place prior to dialysis being required).
- Pre-emptive listing should only occur when a patient reaches eGFR <15 mL/min/1.73m$^{2;}$ and would be expected to be alive in 5 years and to be either on dialysis or starting dialysis within 6 months of joining the waiting list.

ERG critique:

- The ERG recognise that there is uncertainty around this 5% estimate, however would not wish to amend the value given by 3 clinicians independently.

- The ERG also note that even if the 5% is an overestimate (when it may even be an underestimate), this would be ameliorated if all patients assumed to discontinue at 2 years; which both limits the impact, and potentially overestimates the volume of dialysis received (as some rare patients would likely remain dialysis free).

Issue 1: Company proposed population

Following ACM1, the company has updated it's proposed population for imlifidase use based on input from NSHBT and clinical experts

Company proposed population for imlifidase	
Eligibility criteria	• **cRF≥99%, and** • **Matchability Score = 10, and** • **Waiting list time ≥ 2 years, and** • **Proposed dialysis ≥ 2 years (but accepted not a requirement)**
Clinical considerations	• All possible delisting strategies explored • Medically fit to receive a transplant with increased immunological risk • Patient understands and is willing to consider an increased immunological risk transplant
Multidisciplinary team (MDT)	• Patients assessed by a national multidisciplinary team • MDT should develop auditable criteria ensuring imlifidase is allocated to patients who would otherwise be unlikely to receive a transplant

Issue 1: Company proposed population (2)

Company and ERG comments on updated patient eligibility criteria

Company comments:

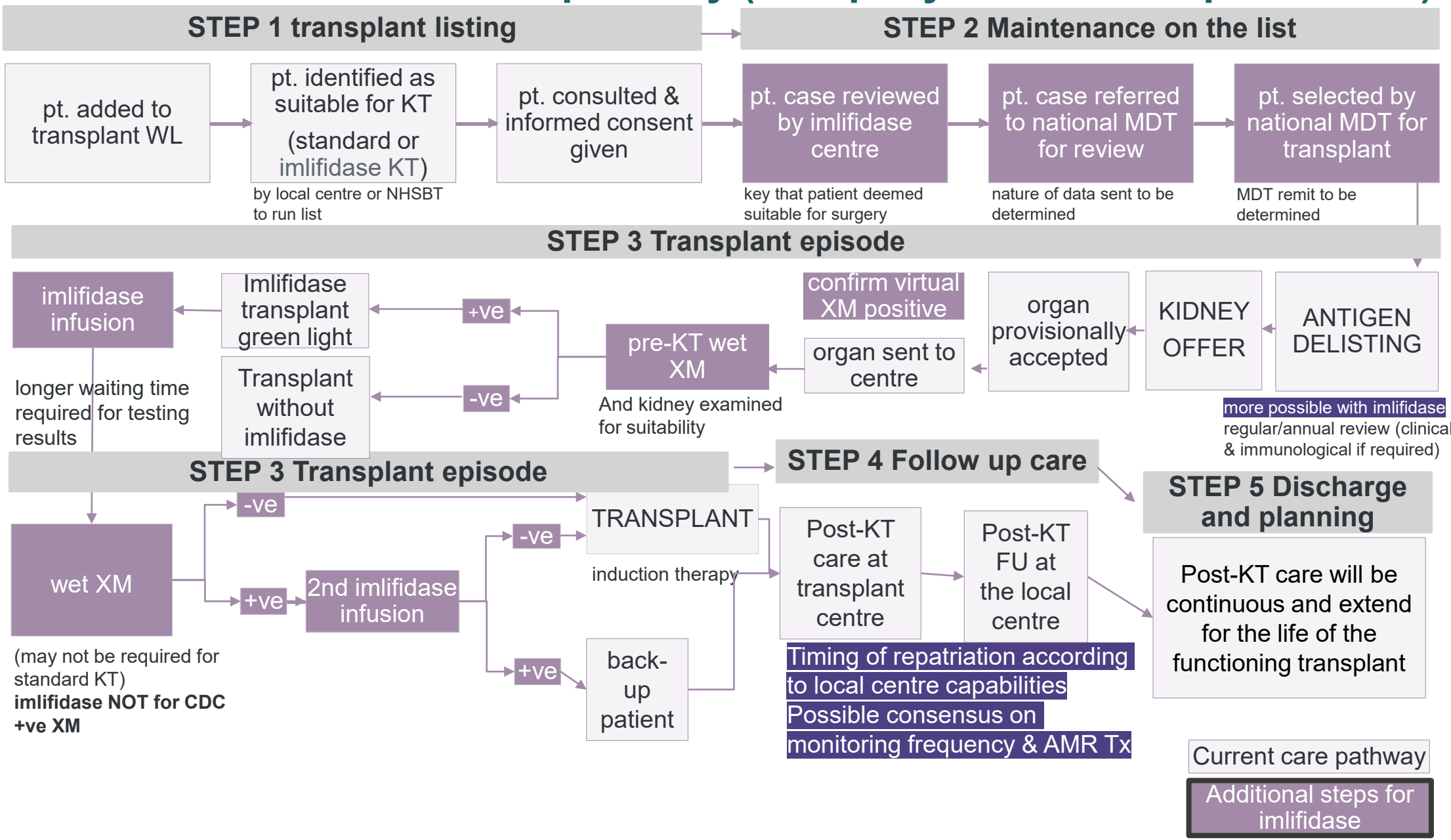
- Updated eligible patient criteria to be more restrictive based on data provided by NHSBT and clinical expert feedback
- Requirement for being on the waiting list for ≥2 years allows for kidney offering scheme to find a suitable organ without imlifidase, and is longer than the median waiting time for all adult UK kidney transplantation patients (633 days).
- Estimated that the % of Tier A patients on the waiting list for ≥2 years who are not on dialysis is very small or zero

ERG comments:

- Proposal provided more certainty but requiring dialysis for ≥2 years is unrealistic (unclear if validated by clinical experts + requirement may lead to unnecessary dialysis)
  - A small number (~5%) would meet all other criteria but may not be on dialysis (e.g. pre-emptive listing or contraindication).
- ERG clinical experts stated that other eligibility criteria appropriate and may be refined in practice with further experience with imlifidase, for example starting with cRF = 100%
- Only XX patients in the company's trials meet company's updated patient criteria, therefore there is uncertainty about the generalisability of the evidence.

◉ Is the company's proposed population appropriate?

Issue 2: Possible treatment pathway (Company submission post ACM1)

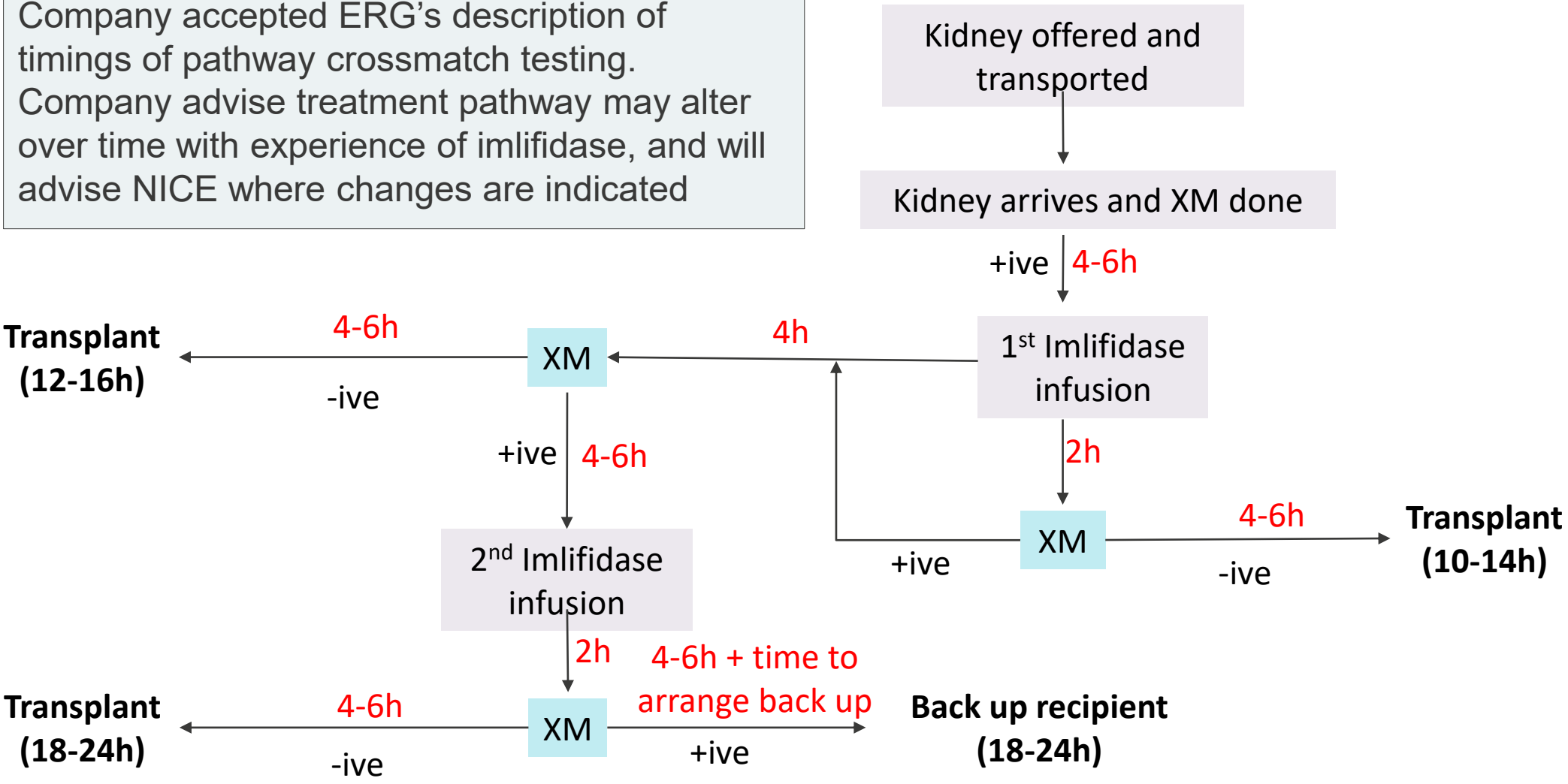


Abbreviations: AMR: antibody-mediated rejection; CDC: complementary dependent cytotoxicity; FU: follow-up; KT: Kidney Transplant; MDT: multidisciplinary team; NHSBT: NHS Blood and Transplant; pt: patient; tx: treatment; WL: waiting list; XM: crossmatch; -ve: negative; +ve: positive

Source: Company's revised submission

Issue 2: treatment pathway with crossmatch testing timings

Company accepted ERG's description of timings of pathway crossmatch testing. Company advise treatment pathway may alter over time with experience of imlifidase, and will advise NICE where changes are indicated



Issue 2: treatment pathway

Company and ERG comments on updated treatment pathway

Company comments:

- Engaged with clinical experts to determine how imlifidase could be integrated into current care pathway
- Clinical experts felt that proposed pathway would allow imlifidase-enabled transplants to be conducted within an acceptable cold ischaemia time (CIT).
- Input from clinical advisory board suggested that immunosuppression regimen would be equivalent to that required for HLA incompatible transplants.

ERG comments:

- Acknowledge treatment pathway may change with experience. Appropriate reviews are undertaken. However, changes to pathway may impact clinical outcomes.
- Clinical advice suggested that impact of crossmatch testing on CIT may be reduced if clinicians are able to save time in other areas of the treatment pathway
- Some people treated with imlifidase may have CIT >24 hours (timepoint of concern)
- Some centres may arrange a 'backup patient' to reduce kidney wastage
- Some small risk of wastage of the kidney may be acceptable to clinicians, as a small risk of wastage currently accepted within the KOS.

- ***Is the company's proposed treatment pathway appropriate?***
- ***Are the company's proposed timings of crossmatch tests (XM) appropriate?***

Issue 3 – Updated clinical data

The company have provided additional clinical data from an ongoing trial and resubmitted further clinical data from their original submission

Further trial data (Study 14)

- Interim data from ongoing study
- Follow-up data provided up to 3 years (previous submission included data up to 2 years)
- N=39 (13 had cPRA ≥99%, [redacted] met the company's updated population)
- The company also outlined details of a post-authorisation efficacy and safety (PAES) study

Resubmitted trial data

- Committee and ERG had concerns with the quality of submitted evidence at ACM1
- Company have revised and resubmitted data on the following:
  - Crossmatch conversion
  - MFI levels
  - Transplant rejection
  - Graft survival

New data used in updated company base case

- Graft survival (unlikely to be transplanted group, extrapolated with an exponential distribution)
- Overall Survival with a functioning graft (all imlifidase group, extrapolated with an exponential distribution)

Issue 3 – Updated clinical data (2)

Results from the '3-year' follow-up study (Kjellman et al. 2021)

Characteristics	XM+, (n = 39)	XM+, DD and cPRA ≥ 99.9%, (n = 13)
Survival		
Death-Censored Allograft Survival at 3 years	84%	92%
Patient Survival at 2 years	90%	NR
Patient Survival at 3 years	90%	NR
AMR		
14 days	NR	5/13 (38%)
1 month	11/39 (28.2%)	NR
6 months	15/39 (38.5%)	7/13 (53.8%)
AMR-mediated graft loss	NR	0%

Results from the '3-year' follow-up data in the new eligible patient population and the 'unlikely to be transplanted' population

Characteristic	New eligible patient population (n=x)	'Unlikely to be transplanted' population (n=19)
Rate of AMR (x/XX, %), in Follow-up trial	x xxxx	x xxxx
Rate of chronic AMR (x/XX, %)	x xxxx	x xxxx
Rate of CMR (x/XX, %)	x xxxx	x xxxx
Rejection leading to graft loss (x/XX, %)	x xxxx	x xxxx
Number of patients receiving treatment for AMR (x/X, %)	x xxxx	x xxxxx
Graft survival (median and 95%CI) at 3 years	xxx xxxxx xxxxx	xxx xxxxx xxxxx
Survival with functioning graft (median and 95%CI) at 3 years	xxx xxxxx xxxxx	xxx xxxxx xxxx
Patient survival (median and 95%CI) at 3 years	xxx xxxxx xxxxx	xxx xxxxx xxxx

Issue 3 – Updated clinical data (3)

Company resubmitted and revised data	Newly defined population	'unlikely to be transplanted'	'All imlifidase' population
Sample size	[redacted]	[redacted]	[redacted]
Overall rate of crossmatch conversion (x/X, %)	[redacted]	[redacted]	[redacted]
Overall rate of crossmatch conversion using FACS (x/X, %)	[redacted]	[redacted]	[redacted]
Number of patients who received 2 regimens of imlifidase	[redacted]	[redacted]	[redacted]
Total number of crossmatch tests conducted* (per person)	[redacted]	[redacted]	[redacted]
(FC) crossmatch tests conducted** (per person)	[redacted]	[redacted]	[redacted]
Number of patients who received a transplant after treatment with imlifidase (x/XX, %)	[redacted]	[redacted]	[redacted]
Rate of AMR (x/XX, %), in Original trials	[redacted]	[redacted]	[redacted]
Rate of chronic AMR (x/XX, %), in Original trials	[redacted]	[redacted]	[redacted]
Rate of cell-mediated rejection (x/XX, %), in Original trials	[redacted]	[redacted]	[redacted]
Rejection leading to graft loss (x/XX, %), in Original trials	[redacted]	[redacted]	[redacted]
Number of patients receiving treatment for AMR (x/X, %), in Original trials	[redacted]	[redacted]	[redacted]
Overall survival at final follow-up (x/X, %), in Original trials	[redacted]	[redacted]	[redacted]
Graft survival (median and 95%CI) at 6 months	[redacted]	[redacted]	[redacted]
Survival with functioning graft (median and 95%CI) at 6 months	[redacted]	[redacted]	[redacted]
Patient survival (median and 95%CI) at 6 months	[redacted]	[redacted]	[redacted]
Number of patients whose MFI levels remained above 3000 at all measured timepoints (x/XX, %)	[redacted]	[redacted]	[redacted]
Rate of re-transplant (x/XX, %)	[redacted]	[redacted]	[redacted]

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* only physical XM included, B or T-cell at same time counted as same test, CDC and FC counted as separate tests

** only FCXM included, B or T-cell at same time counted as same test

Issue 3 – Updated clinical data (4)

ERG comments on company's updated and resubmitted data

	ERG comments
ERG view on new data (data up to 3 years follow-up)	• Quality limited: small numbers met company's refined population (n=[redacted]). Only 6/13 (46%) with cPRA ≥ 99.9% and available at 3-years follow-up. Limited number of outcomes available. • Best evidence remains limited to original trial data. • Clinical advice to ERG stated longer term data (>3 years) required
Notes on new data	• Clinical advice ERG expected graft survival drop in subsequent years (and poorer compared to graft survival for non-sensitised patients) • Clinical advisors expect higher mortality with greater sensitisation, due to increased immunosuppression burden
Notes on resubmitted data	• Only [redacted] in trials met company's refined population, creates uncertainty. • Sizeable minority got a crossmatch conversion after [redacted] • Uncertain to what extent data on MFI levels are meaningful • Newly defined population: [redacted] antibody-mediated rejection (AMR). v other trial populations ([redacted]). Clinical experts concerned by high rates • Comparable graft survival for new population v other trial populations - length of follow-up may be too short to show meaningful differences

ERG notes that company have repeatedly refused to provide infection data and consider this a major omission, as infection risk is important for clinical, cost and treatment decision considerations

◉ Does the additional and resubmitted clinical data from the company reduce the uncertainty in the evidence base?

Issue 4 – company updated modelling assumptions

The company have revised their base case analysis following ACM1

Company's updated base case		ERG comments
Utility values	Values from Li et al 2017 (UK study)	Accept company's choice. Notes a lack of utility data for people treated with imlifidase (or highly sensitised population in general)
% receiving transplant with imlifidase	96.3% - estimated from the trial data (2 patients did not receive a transplant)	Accept company choice but noted uncertainty - 1 patient did not achieve negative crossmatch (but had transplant) 94.4% rate used in sensitivity analysis but ERG consider either proportion is reasonable
% receiving transplant in comparator arm	xxxxx based on NHSBT analyses based on proposed patient population	Agree updated annual rate is appropriate and matches company's refined population
Costing	Dialysis type: NHSBT, 1 crossmatch test per dose, Inclusion of DSA test costs	Agree with revisions to model type of dialysis (disagree with proposed dialysis requirement in proposed eligibility criteria). ERG apply costs of xxxx xxxxxxxxx xxxxx xxxxx xxxx xxx xxxxxx xxxxxxxxxx but considered costs could range up to xxx tests

Issue 4 – company updated modelling assumptions (2)

Graft survival predictions – key model driver

Company's updated base case			
Graft survival	Updated trial data (up to 3 years) using 'unlikely to be transplanted' population		
	iBox predictions, with Weibull extrapolation (Original company base case)	**Unlikely to be transplanted, with exponential extrapolation (revised company base case)**	**iBox predictions, with Weibull extrapolation, 0.9 HR applied (ERG preferred assumption)**
5-year survival	XXX	XXX	XXX
10-year survival	XXX	XXX	XXX
20-year survival	XXX	XXX	XXX

ERG comments

- 3 year trial data is still too immature.
- New company approach predicts better outcomes v previous iBox method (considered too optimistic) with very little data used to inform extrapolation (n=6 at 3 years).
- ERG use 0.9 HR applied to iBox method due to lack of appropriate data.
- Noted log-cumulative hazard plots suggest neither extrapolation appropriate and given scarcity of data it is unlikely any parametric extrapolation would produce reasonable long-term estimate so sought clinical opinion.

ERG clinical expert opinions

- Expect graft survival to drop in subsequent years and be poorer than graft survival for non-sensitised patients.
- Longer follow-up data needed to establish whether graft survival would be comparable with patients who receive a transplant following other de-sensitisation regimes.

Issue 4 – company updated modelling assumptions (3)

Additional issues identified by the ERG:

Overall survival (OS) with a functioning graft

- Use of trial data to inform OS with a functioning graft a key limitation - adds great uncertainty. The OS data were too immature to produce reasonable long-term estimates for a lifetime horizon. Better data could be used to inform this parameter (e.g. informed by highly-sensitised population from literature or NHS data) ERG explored using 'unlikely to be transplanted' OS data in scenario analysis.

Subsequent transplant

- Some patients able to have another transplant. Imlifidase can only used in one transplant, so further transplants would be without desensitisation therapy. Costs and efficacy of retransplant not considered in model. No retransplants occurred in trials but follow-up short

◉ ***What are the most appropriate modelling assumptions?***

Issue 5: Equality considerations

The committee was aware of several potential equality issues at ACM1

Issue	Description
Impact on minority ethnic groups	People with protected characteristics may have difficulty accessing a matched donor kidney without imlifidase. Committee were unsure if this was because this group are highly sensitised at a higher rate, or because the available donor pool of suitable kidneys for this population is smaller than for other people who are highly sensitised
People who have become highly sensitised through pregnancy	One of most common causes for a person to be highly sensitised with HLA is previous pregnancy. This population less likely to receive a suitable living donor kidney. For people who are most sensitised, 10-year survival results differ (67% to 68% for men compared with 15% for women). Plausible that people who have become highly sensitised through pregnancy may have additional benefit through imlifidase
People who would have otherwise had a kidney transplant	Potential for harm for individuals who would have had a kidney without imlifidase, but may not get a kidney if imlifidase introduced. Issue underlines importance of a well-defined population for imlifidase use. Impact of imlifidase on kidney waiting lists needs to be considered.

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◉ Are there any potential equality issues that should be taken into account in decision-making?

Issue 6 - Opportunity cost

There is a finite number of kidney donors. The committee considered at ACM1 that recommending imlifidase requires claims of fairness and equality for highly sensitised people to outweigh additional costs and loss of benefits to people not highly sensitised

Company comments (ACM1):

- Major advantage of imlifidase is greater equality of access to kidney transplant ('equity in provision of transplant')
- Longer/indefinite time on dialysis associated with declining health and quality of life
- Utilitarian cost-effectiveness analysis on whole population level wouldn't capture this benefit
    - also fails to consider allocation of deceased donor kidneys through KOS already relies on trade-off between equality of access and providing best 'quality' matching
- Despite recent KOS changes having equality improvements, there are disadvantaged people who do not benefit from aims of scheme, remain unlikely to have transplant

ERG comments:

This key issue of perspective remains. Analysis presented takes the decision point to be whether to give imlifidase in context of individual highly sensitised patients; and does not include the counterfactual outcomes that could have been obtained by the [scarce] kidney in a non-sensitised patient – which would require a population level model.

◉ ***Should the committee consider the opportunity cost resulting from imlifidase use?***

Innovation

Professional submissions:

- Could provide significant benefit to selected patients.
  - Need to identify target population, integrate use into UK allocation policy, standardise H&I practice and protocolise treatment of antibody recurrence and acute antibody mediated rejection
- Potentially a step-change in the management of the condition

Company comments:

- Company considers imlifidase to be highly innovative
- No other available treatments are able to rapidly and specifically remove IgG
- Step-change in therapy. Provides a rapid and effective desensitisation treatment allowing for successful transplant within the time window of a deceased donor organ in people who would have otherwise been unlikely to receive a transplant
- Addresses important equality issues by increasing access to kidney transplants

◉ ***is imlifidase considered innovative?***

Future imlifidase clinical data

Further clinical data for imlifidase is expected to become available

Ongoing studies (source original company submission)

- Long-term follow-up study (17-HMedIdeS-14) for all patients transplanted in the 4 clinical trials (13-HMedIdeS-02, 13-HMedIdeS-03, 14 HMedIdeS-04, and 15-HMedIdeS-06) is ongoing.
- May include up to 46 patients
- Follow-up for up to 5 years
- Outcomes include kidney function, graft survival and patient survival
- Final study visit exoected Q4 2022, and final study report expected Q4 2023

Post-Authorisation Efficacy and Safety (PAES) study

- Planned phase III controlled, non-randomised, open-label study
- Data will support full marketing authorisation in EU and UK
- 50 patients (highly sensitised, highest unmet need) will be treated with imlifidase
- primary endpoint: [redacted]
- Secondary endpoints include [redacted]

NICE ◉ *Would additional clinical data resolve uncertainty?*

Potential for market access arrangements

- Managed access team consider that there are important barriers to making a recommendation for managed access for this topic:
  - Managed access is not appropriate to explore uncertainty around patient eligibility or treatment pathway. Principle of managed access is that the entire eligible population as recommended by NICE have access to the treatment.
  - There are ethical issues to making a managed access recommendation, technically a negative recommendation, when there are a finite number of kidney donors.

- If managed access were still to be considered, the MA team highlight:
  - The MA team consider the ongoing studies are unlikely to provide meaningful additional data for committee decision-making
  - It is unlikely that data collected in clinical practice could provide a robust alternative source to inform long-term graft survival
  - Whilst feasible to collect, the MA team would need time to explore collecting relevant outcomes with NHSBT e.g. proportion who receive transplant or 2nd dose

Key assumptions in company and ERG analyses

The company and ERG key assumptions are described below

Parameter	Base case		Sensitivity/scenario analysis
	Company	ERG	
% requiring a second dose of imlifidase	xxx% - Total safety set (n=54)		**ERG**: xxx%: estimated safety set % x%: unlikely to be transplanted data xxxx%: new population data
% imlifidase to get a transplant	96.3% - Total safety set (n=54).		**ERG**: 94.4% (achieved a negative crossmatch following imlifidase)
OS (functioning graft)	All imlifidase data (n=46): exponential distribution		**Both**: Unlikely to be transplanted data (n=25) - exponential distribution
Utilities	Li et al. (2017)		**ERG**: Cooper et al. (2020)
Graft survival	Unlikely to be transplanted (n=25) – exponential distribution	iBox predictions – Weibull distribution with 0.9 HR	**Company**: iBox predictions - Weibull **ERG:** iBox predictions with 0.8, 0.85, 0.95 HR applied and unlikely to be transplanted (n=25) - exponential distribution **Both**: All imlifidase (n=46) - Extrapolated with an exponential distribution
% comparator transplant rate	NHSBT data	NHSBT data	**ERG***:* 5%, 10% and 15% annual transplantation rates
Crossmatch tests (number)	1 (assumption)	xxxx – All imlifidase data (n=46) –FCXM tests minus 1	**ERG**: 1 (assumption) xxx– All imlifidase data (n=46): physical FCXM tests minus 1

Cost effectiveness results: company

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case:			
• [redacted]% receive second dose; • 96.3% receiving imlifidase get transplant; • unlikely to be transplanted 3-year data used with exponential extrapolation for graft survival; • all imlifidase data - extrapolated with exponential distribution for OS with a functioning graft	[redacted]	[redacted]	**27,754**
Company base case probabilistic ICER (ERG corrected)	[redacted]	[redacted]	**29,210**
Graft survival:			
iBox	[redacted]	[redacted]	**32,863**
All imlifidase population 3-year data	[redacted]	[redacted]	**28,962**
Time horizon:			
10 years	[redacted]	[redacted]	**75,605**
20 years	[redacted]	[redacted]	**35,596**
OS with a functioning graft:			
Unlikely to be transplanted 3-year data	[redacted]	[redacted]	**46,309**

Cost effectiveness results: ERG

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base case			
• 5% of SoC to receive 'no dialysis'; • increase number of crossmatch tests to 2.4; • use iBox predictions to inform graft survival with a 0.9 HR; • all imlifidase data - extrapolated with exponential distribution for OS with a functioning graft	[redacted]	[redacted]	**37,525**
ERG base case probabilistic ICER	[redacted]	[redacted]	**38,971**
Graft survival:			
iBox predictions with 0.8 HR	[redacted]	[redacted]	**41,764**
iBox predictions with 0.85 HR	[redacted]	[redacted]	**39,503**
iBox predictions with 0.95 HR	[redacted]	[redacted]	**35,783**
Unlikely to be transplanted 3-year data (company preferred)	[redacted]	[redacted]	**29,482**
OS with a functioning graft:			
Unlikely to be transplanted 3-year data	[redacted]	[redacted]	**62,323**

Cost effectiveness results: ERG

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base case	[redacted]	[redacted]	**37,525**
ERG base case probabilistic ICER	[redacted]	[redacted]	**38,971**
Time horizon			
10 years	[redacted]	[redacted]	**93,117**
20 years	[redacted]	[redacted]	**46,679**
SoC Transplant rate ([redacted]% in base case)			
5%	[redacted]	[redacted]	**33,540**
10%	[redacted]	[redacted]	**40,370**
15%	[redacted]	[redacted]	**48,446**
% receiving 2nd regimen of imlifidase ([redacted]% in base case)			
[redacted]	[redacted]	[redacted]	**42,181**
% receiving transplant after imlifidase (96.3% in base case)			
90%	[redacted]	[redacted]	**42,866**
Alternative utility source			
Cooper et al (2020)	[redacted]	[redacted]	**37,977**

Key issues

Key issues for ACM2	Impact
1: Population	
• Is the company's new proposed population for imlifidase use appropriately defined?	
2: Treatment pathway	
• Is the proposed imlifidase positioning in the treatment pathway appropriate? Are there any issues with the proposed crossmatch testing schedule?	
3: Updated clinical data	
• Does the additional data submitted reduce uncertainty in the analysis?	
4: Company's updated modelling assumptions	
• What are the most appropriate modelling assumptions/sources?	
5: Potential equality issues	
• Are there any equalities issues that need to be addressed?	
6: Scope of the appraisal	
• Should the committee consider the costs and benefits of kidney transplant in those not eligible to have imlifidase?	

 Model driver  Small impact  Unknown impact

Unresolved | Some discussion | Resolved