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]

ACM-3 Chair's presentation

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Company: Hansa Biopharma

ERG: PenTAG

Meeting: 05th May 2022

Key clinical and cost-effectiveness issues

Has all relevant clinical evidence been considered and is this robust enough for decision-making?	
Would the impact of using imlifidase on cold-ischaemic time be unacceptable?	
Should graft survival projections be estimated using iBox?	
Have all relevant equalities issues been considered in decision-making?	

Appraisal history

RECAP

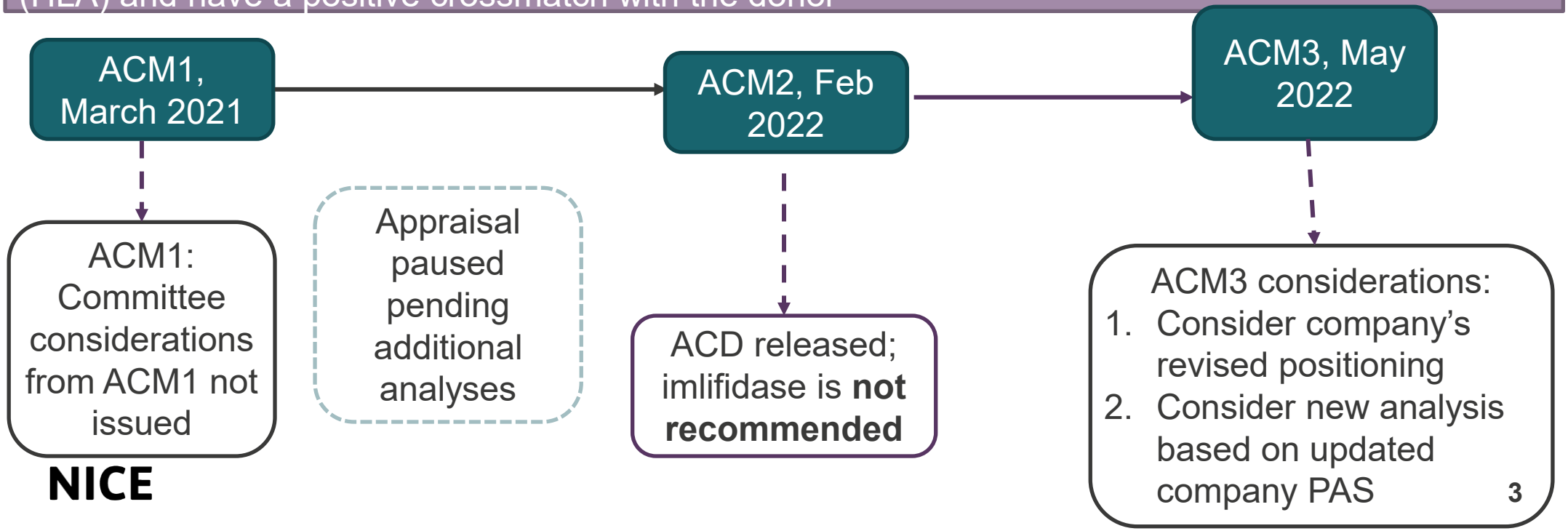
Conditional Marketing authorisation*

For desensitisation treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor. Use should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitized patients

*** Conditional marketing authorisation based on submission of longer- term efficacy data on graft survival by Dec 2023, and 1 year graft survival rates after desensitization by Dec 2025**

ACD recommendation:

Imlifidase is not recommended, within its marketing authorisation, for adults who are waiting for a kidney transplant from a deceased donor, who are highly sensitized with human leukocyte antigens (HLA) and have a positive crossmatch with the donor



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Clinical data

Before ACM2 company provided further data and analyses

Further trial data

- Interim data from ongoing study
- Follow-up data provided up to 3 years (previously was up to 2 years)
- N=39 ([redacted] met the company's updated population)
- The company also mentioned an updated post-authorisation efficacy and safety (PAES) study. This has been finalised but no data is available as yet to contribute to this appraisal

Resubmitted trial data

- Following concerns with quality of submitted evidence at ACM company resubmitted data at ACM2

Company provided evidence for 3 populations:

- Everyone in trials (all imlifidase)
- Most relevant (unlikely to be treated)
- Newly defined population

ERG view on company's data submitted at ACM2

- Quality limited: small numbers met company's refined population
- Limited number of outcomes available
- Best evidence remains limited to original trial data
- Clinical advice to ERG stated longer term data (>3 years) required

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	[redacted]	[redacted]
Rate of chronic AMR (x/XX, %)	[redacted]	[redacted]
Rate of CMR (x/XX, %)	[redacted]	[redacted]
Rejection leading to graft loss (x/XX, %)	[redacted]	[redacted]
Number of patients receiving treatment for AMR (x/X, %)	[redacted]	[redacted]
Graft survival (median and 95%CI) at 3 years	[redacted]	[redacted]
Survival with functioning graft (median and 95%CI) at 3 years	[redacted]	[redacted]
Patient survival (median and 95%CI) at 3 years	[redacted]	[redacted]

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

Considerations at ACM2 (1)

RECAP

Committee conclusion	ACD	Comments at consultation
Renal replacement therapies while waiting for a kidney transplant can have a substantial effect on quality of life	3.1	Agreement about detrimental impact of CKD
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	3.3	Agree other desensitisation regimes are not alternative to imlifidase
Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people	3.4	Company suggest consequence of immunosuppression preferable to impact without transplant but had no data for this and currently have no QoL data
Proposed treatment pathway underestimates impact on CIT of donor kidney	3.6	Company responded
Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitized	3.7	Company responded

ACD: Appraisal consultation document, CE: cost-effectiveness CIT: Cold ischaemic time; CKD: chronic kidney disease; QoL Quality of life

Considerations at ACM2 (2)

RECAP

Committee conclusion	ACD	Comments
Available outcome data is currently too short term to decide whether imlifidase can be used in the NHS	3.8	Company responded
Some AMR is expected but people who are highly sensitized may have better outcomes if they wait for a match in the new algorithm	3.9	Company responded
Data shows that some people for whom imlifidase might be suitable already have access to transplants	3.11	Company responded
Not everyone who has imlifidase treatment goes on to have a kidney transplant but the exact proportion is uncertain	3.12	ERG consider proportion is uncertain but small changes impact ICER
Graft survival projections from iBox are highly uncertain so a hazard ratio should be applied to account for this	3.13	Company prefer 3 yr data; ERG prefer iBox with HR adjustment
Imlifidase could provide a step-change in treatment but there are challenges for implementation	3.19	Company responded
A managed access agreement is not appropriate	3.20	Company note PAES study will provide useful evidence for decision-making when it is available

ACD: Appraisal consultation document, AMR: Antibody-mediated rejection;

ACD consultation

Consultation comments

- Company (Hansa)
  - Provided consultation comment responses and a revised base case
  - Updated patient access scheme
- Professional Groups
  - UK Kidney Association
  - British Transplant Society
  - NHS England and Improvement
- Web comments
  - 5 web comments received
    (NHS Blood & Transplant (x2); Belfast Trust HSC; North Bristol NHS trust; University Hospitals Coventry and Warwickshire)

Clinical evidence

ACD:
Section 3.8 *ERG considered quality of data beyond original trials was limited. Committee conclude available outcome data is currently too short term*
Section 3.9 *There was a high rate of AMR (40%) in the company's original clinical data*

Company:

- *3 year follow up data is robust and longest-term data in highly sensitized*
- *Uncertainty diminished because efficacy and safety consistent across subgroups and data was enough to grant conditional marketing approval*
- *In 3-year follow up data, overall incidence of AMR = 38% (5/13), A 10% AMR aligned to incidence in compatible transplant setting*

ERG response:

- Only small number provided data at final 3-year follow-up - Clinical opinion longer follow-up is needed
- Conditional marketing only when insufficient evidence for full authorisation
- Do not consider issue about AMR has been addressed by the company

Consultation comments:
NHSE&I: *3 year data shows comparable outcomes to other highly sensitized patients*
Agree more data required – this would be acquired if imlifidase were adopted
British Transplant Society: *long-term outcomes data is limited, but 3-year outcomes reported are at least as good as those in antibody incompatible live donors*
*AMR is inevitable – and close to 40% in highest risk (*sufficient donor specific antibodies for positive CDC cross match).
Web comment: *AMR with imlifidase is expected to be around 40% but 10% would be consistent with a standard risk transplant (antibody compatible). Some comments suggest post-imlifidase outcomes similar to post plasmapheresis (published in Krishnan et al) but 1 comment notes plasmapheresis is not possible in deceased donations*

Has all relevant clinical evidence been considered and is this robust enough for decision-making?

Impact on cold-ischaemic time (CIT) (1)

ACD:

Section 3.6

- *In the ERG pathway estimated CIT varied between 10 to 24 hours (based on number of infusions and number of crossmatch tests needed)*
- *A CIT of more than 24 hours means kidney effectively becomes unusable for transplant*
- *A 2nd imlifidase infusion would add an unacceptable amount of time to life of kidney*
- *There could be differences between non UK centres in trials and UK NHS practice leading to differences in CIT estimates*

Company response:

- *Does not agree that using imlifidase leads to unacceptable CITs and organ wastage*
  - *CIT is unlikely to reach upper bounds of range estimates*
  - *Kidneys do not automatically become unusable at 24-hours*
  - *UK clinicians report they transplant kidneys with a CIT ≥ 24 hour*
  - Crossmatch turnaround time in ERG pathway was 6 hours but Company suggest time could be from 2 to 4 hours
  - *In Company's trials nearly all patients only had 1 imlifidase infusion (93.5% had crossmatch conversion after 1 dose) adjusting eligibility criteria may reduce likelihood of a 2nd dose*
  - *Although UK clinicians report imlifidase will increase CIT in most cases, this is not a barrier for use*
  - *NHSBT data shows transplants being performed with >24 hours CIT and that many deceased donor transplants with a CIT >20 hours have been successful*
  - *Data suggest variations in mean CIT in USA based transplant centres is* [redacted] *than in EU based centres* [redacted]

Impact on cold-ischaemic time (CIT) (2)

ERG response

- *ERG rationale unchanged*
- *Maintain estimates in ERG pathway are plausible and based on input from clinical advisors but is unable to revise its critique without firm data to inform how the proposed treatment pathway may altered*
- *Clinical experts at NICE committee felt ERG timeline could be further extended to account for potential pressures in health service that may further extend CIT.*
- *ERG still consider longer CIT is plausible due to need for a 2nd dose, - may have poorer transplant outcomes- ERG carried out additional scenario on number having 1 dose only - ERG ICER increased by £951 for first scenario and £2,252 for 2nd scenario*
- *Supports company proposal treatment delivered in a small number of specialist centres – but note time is needed to transport kidneys and recipients to closest centre- ERG unable to validate company data on CIT use in EU and USA based centres*

Consultation comments:

NHSE&I*: CIT time >24 hours untrue for deceased after brain death donors (based on NHSBT data)*

British Transplant Society*: believe concerns over CIT and risk of a kidney waste is unfounded*

UK Kidney Association*: Access to machine perfusion technologies could be used to preserve the organ during the cross-match assessment*

Impact on cold-ischaemic time (CIT) (2)

Web comments:

- Agree CIT might be > 12-18 hours but can be mitigated and suggest risks of CIT are overstated in the ACD (North Bristol NHS Trust)
- Suggest having a CIT of 36 hours could be used if kidneys are from younger donors (NHSBT)

Several approaches suggested to minimise increase in CIT:

- Use only high quality organ offers (D1 or D2 donor risk quartiles North Bristol NHS Trust)
- Adjusting eligibility criteria could alter number of crossmatch tests needed (North Bristol NHS Trust)
- Cross-match testing should be done before donor organ arrives (using pre-transplant samples and virtual crossmatches (North Bristol NHS Trust)
- Consider machine perfusion for kidneys intended for those eligible for imlifidase (University Hospitals Coventry & Warwickshire)
- Mandate need for backup recipient, who should only be transplanted if:
    1. First patient has an adverse reaction to imlifidase
    2. after the first dose the cross match remains positive. (However, experienced centres in antibody-incompatible transplant (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
    3. on very rare occasions after the second dose if the CM does not become negative (University Hospitals Coventry and Warwickshire)

The issue around requirement of a 2nd dose:

- Imlfidase could add 8 to 10 hours to CIT - but concerns about prolonged CIT for 2nd dose ignore benefit in majority who only need 1 dose (University Hospitals Coventry and Warwickshire)
- Suggest that one dose (regimen) be the norm and only give 2nd dose ONLY IF benefits outweigh risk of ↑CIT or delayed graft function ((University Hospitals Coventry and Warwickshire)

Would the impact of using imlifidase on cold-ischaemic time be unacceptable?

Modelling assumptions Graft survival

ACD: Section 3.13

- *Company base case graft extrapolations were based on 3-year follow-up data (n=19)*
- *ERG used iBox predictions and applied HR 0.9 for uncertainty*
- *Committee conclude graft-survival predictions from iBox were highly uncertain.*

Company response:

- Base case assumes 3-year follow up data but applied scenario using iBox to validate
- Comparing long term survival estimates for HLA incompatible transplants were higher than iBox estimates so company conclude no rationale for applying a 0.9 HR to iBox extrapolation

ERG response

- *iBox – was company's preferred source originally*
- *Concerned about generalisability but considered iBox best source given immaturity of trial data*
- *At ACD1, committee considered iBox projection and extrapolation too optimistic – so ERG use 0.9 HR to produce less optimistic projections*
- *Company revised base case used "unlikely to be transplanted" population ERG did not consider this resolves committee concerns around optimistic projections*
- *ERG does not consider NHSBT projections to reflect the graft survival that would be expected in the patients from the imlifidase trials because populations are not aligned and does not consider projections from the HLAi study to reflect population of interest (most based on living donors)*

Consultation comments:

1 web comment suggested estimates using iBox may not be reliable due to complexity of antibody incompatible transplantation.

Should graft survival projections be estimated using iBox?

Equalities, innovation and impact on QoL (1)

ACD

Section 3.1: *People who are on dialysis while waiting for a kidney transplant, have reduced quality of life*

Section 3.7 *The opportunity to ensure highly sensitized patients are treated equally and fairly needs to outweigh additional costs and benefit loss for those not highly sensitized*

Section 3.11 *Some people for whom imlifidase might be suitable will already have access to transplants*

Section 3.18 *Specific consideration needs to be given to people who have become highly sensitized through pregnancy*

Section 3.19 *Imlifidase could provide a step-change but there are challenges for implementation*

Company response:

- *Disagree equity benefit for highly sensitized outweigh benefit loss for non-sensitized patients*
- *Changes to Kidney Offering Scheme will improve but not resolve inequity of access*
- *Committee considerations are not aligned with Principle 9: "our guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged"*
- *Long-term dialysis has significant impact on healthcare costs, morbidity, mortality and QoL*
- *Imlifidase is innovative and can provide an alternative treatment option*
- *Noted comments from patient experts at ACM about burden of dialysis*
- *Not recommending imlifidase goes against 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 (QALYs gained)"*
- *Not recommending imlifidase removes opportunity to improve equity of access for females and highly sensitized patients*

Equalities, innovation and impact on QoL(2)

Consultation comments:
NHS E&I: Highly sensitized patients are currently severely disadvantaged
British transplant society*: Sensitized patients are currently disadvantaged and imlifidase seeks to correct this inequity. Median waiting time for a Tier A patient is likely to be >5 years*
Suggesting a non-sensitized patient may be disadvantaged is not justified
UK Kidney Association: *lack of long-term efficacy data negates concern that NICE may not be fulfilling its commitment to promoting equality of opportunity*
Web comments: *There is no other suitable alternative to reduce HLA antibodies in deceased donation so imlifidase is best option*
Imlifidase could reduce inequity for people with sensitivity due to pregnancy

ERG response

- *NICE committee, company and ERG agree about the detrimental impact of clinical management for CKD*
- *ERG acknowledge pregnancy is one reasons why people may become highly sensitized, but did not identify this as an equality issue*
- *Company suggest committee should consider value imlifidase may offer in providing greater hope for a transplant to people with CKD but have not provided evidence why any benefit would not be captured in utility estimates used in the company and ERG models*
- *ERG accept some uncertainties about implementation but consider uncertainties are relevant to discussion*

Have relevant equalities issues been considered in decision-making?
Should imlifidase be recommended?

Potential for Managed Access

ACD 3.20: A Managed access agreement is not appropriate

Recap: Potential for managed access was discussed at ACM 1

The Nice Managed access team considered:

- *Managed access is not appropriate to explore uncertainty around patient eligibility or treatment pathway*
  - *A principle of managed access is that the entire eligible population have access to treatment*
  - *Highlighted ethical issues to making a managed access recommendation when there are a finite number of kidney donors*
- *MA team consider ongoing studies are unlikely to provide meaningful additional data for decision-making*
  - *It is unlikely data collected in clinical practice could provide robust alternative source to inform long-term graft survival*
  - *MA team would need time to explore collecting relevant outcomes with NHSBT e.g. proportion who receive transplant or 2nd dose*

Consultation comments:

A web comment requested explanation why a managed market access solution not appropriate

- *Notes patient group have no alternative treatment options other than to wait indefinitely, whilst accruing avoidable morbidity with each passing year on dialysis*
- *Managed access allow data gathering to permit evaluation in the NHS setting is critical before arriving at any conclusion on potential benefits to the NHS*

Additional issues

	Notes
People who are highly sensitized wait longer for a suitable donor kidney than those who are not sensitized	• ACD noted a small number could wait up to 7 years" for a transplant, One response suggested this is misleading as some patients wait longer than 7 years and accumulate on waiting list
Modelling assumption- OS with functioning graft	• ERG used "All imlifidase" data in base case in the absence of better data but notes no strong rationale for choosing this over "Unlikely to be transplanted" 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 • ERG notes base case ICERs increase when changing to "Unlikely to be transplanted" data £30,880 (company) and £43,867 (ERG)
Other	• Impact of Kidney Offering Scheme needs to be considered in the model • Cost effectiveness to include immunosuppressive therapies, e.g IVIG and rituximab

Key assumptions in company and ERG analyses

Company and ERG assumptions following consultation

Parameter	Base case	
	Company	ERG
% needing 2nd dose*	[redacted]%	
% imlifidase to get a transplant*	96.3%	
OS (functioning graft)*	All imlifidase data : exponential distribution	
Utilities*	Li et al. (2017)	
% comparator transplant rate*	NHSBT data	
Number of crossmatch tests**	2.42	
Proportion in standard care not having dialysis**	5%	
Graft survival ***	Unlikely to be transplanted data 3-yr follow-up– exponential distribution	iBox predictions – Weibull distribution with 0.9 HR

*ERG and company previously reached agreement on these assumptions
** Company have amended base case following ACD consultation
*** Company and ERG retain original position following ACD consultation

Cost effectiveness: Base

Arm	Total			Incremental			
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	ICER (£/QALY)
Company base case (deterministic)							
Imlifidase	[redacted]	[redacted]	[redacted]			-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,725
ERG base case (deterministic - Uses iBox predictions to inform graft survival with a 0.9 HR)							
Imlifidase	[redacted]	[redacted]	[redacted]			-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,014

	Incremental		
	Costs (£)	QALYs	ICER (£/QALY)
Company base case (probabilistic)			
Imlifidase	[redacted]	[redacted]	£22,009
ERG base case (probabilistic- (Uses iBox predictions to inform graft survival with 0.9 HR)			
Imlifidase	[redacted]	[redacted]	£29,462

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*Results include company PAS discount

Cost effectiveness: Company scenario analyses

Company presented 8 scenarios all except Graft loss extrapolation using Krishnan et al have previously been presented by the company

Results show comparison using company analyses and ERG preferred analyses

Scenario	ICER (£/QALY)	
	Company	ERG
Time horizon – 10 years	£55,132	£68,945
Time horizon – 20 years	£24,933	£34,048
Graft loss extrapolation – iBox	£25,214	£25,214
Graft loss extrapolation – All imlifidase patients	£21,014	£21,014
Graft loss extrapolation – Krishnan et al.	£18,723	£18,723
OS with a functioning graft – 'Unlikely to be transplanted' patients	£30,880	£43,867
No caregiver disutility	£21,396	£28,937
Caregiver disutility source – Nagawasa et al (2018)	£21,115	£28,551

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Results include company PAS discount

Cost effectiveness: ERG scenario analyses

ERG considered various scenario analyses all have previously been presented

Results show comparison using company analyses and ERG preferred analyses

Scenario	ICER (£/QALY)	
	Company	ERG
Utility source – Cooper *et al* (2020)[4]	£21,028	£28,351
Proportion of imlifidase receive a transplant – 94.4%	£21,827	29,276
Proportion of imlifidase receive a transplant – 90%	£24,691	£32,559
Proportion of imlifidase receive a transplant – 99%	£19,204	£26,270
SoC annual compatible transplant rate – 5%	£17,780	£24,617
SoC annual compatible transplant rate – 10%	£22,827	£30,439
SoC annual compatible transplant rate – 15%	£28,795	£37,324
SoC proportion on 'no dialysis' – 0%	£20,014	£27,229
SoC proportion on 'no dialysis' – 10%	£21,437	£28,798
Number of crossmatch tests after full dose of imlifidase - 1	£20,591	£27,860
Number of crossmatch tests after full dose of imlifidase – 5	£20,884	£28,196
Number of DSA tests - 1	£20,448	£27,731
Number of DSA tests - 6	£21,140	£28,438
Apply HR to iBox graft estimates – 0.80	£31,627	£31,627
Apply HR to iBox graft estimates – 0.85	£29,699	£29,699
Apply HR to iBox graft estimates – 0.95	£26,530	£26,530
Proportion of imlifidase patients to receive a second dose – [redacted]%	£21,128	£28,476
Proportion receive second dose – [redacted]%	£21,392	£28,777
Proportion of receive a second dose xxxx%	£24,184	£31,974
Apply alternative transplant cost - £21,000	£22,042	£29,528
Change OS dialysis source – ERA-EDTA	£23,849	£30,232
Apply HR to "Unlikely to be transplanted" graft survival – 0.9 **£	£22,811	£22,811
Apply HR to "Unlikely to be transplanted" graft survival – 0.98 **	£21,105	£21,105

Results include company PAS discount

Cost effectiveness: ERG scenario analyses

At PMB ERG carried out 2 Scenarios to assume 0% received a 2nd dose and those needing a 2nd dose remain on dialysis

1. Based on proportion assumed to have imlifidase but no subsequent transplant in trials
2. Based on proportion assumed to have imlifidase but no subsequent transplant in trials but allowing for 1 patient who did not achieve a negative FACS crossmatch but had transplant

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

Results include company PAS discount

Key clinical and cost-effectiveness issues

Has all relevant clinical evidence been considered and is this robust enough for decision-making?	
Would the impact of using imlifidase on cold-ischaemic time be unacceptable?	
Should graft survival projections be estimated using iBox?	
Have all relevant equalities issues been considered in decision-making?	