NICE National Institute for Health and Care Excellence

Slides for public – fully redacted

# Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease

# Lead team presentation


Lead team: Sofia Dias, Rebecca Harmston, Guy Makin

ERG: PenTAG

Technical team: Gary McVeigh, Amy Crossley, Christian Griffiths, Jasdeep Hayre

Company: Hansa Biopharma


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# Key issues unresolved

**Issue 2:** Are there any potential changes to the treatment pathway and current allocation scheme that need to be considered in decision making?

**Issue 3:** Should a matched comparison be carried out to strengthen the clinical evidence? Is evidence in UK patients/NHS context needed for decision making?

**Issue 4:** Is the clinical efficacy evidence presented by the company valid and sufficient for decision making?

**Issue 5:** Should any of the clinical effectiveness data be provided in a different way to enable validation of clinical effectiveness estimates?

**Issue 6:** Which values should be used for:
a) proportion of people treated with imlifidase who have a transplant?
b) proportion of people in comparator arm who have a transplant without imlifidase?

**Issue 7:** Should the model use the company's base case utility values, or those sourced from the Cooper et al. systematic review of utility values?

**Issue 1*:** Should the appraisal consider the costs and benefits of kidney transplant in those not eligible to have imlifidase?



**NB, issues not in same order in slides as during technical engagement*

# 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**

**4,647 adults on UK kidney transplant waiting list (March 2019)**

**2,329 adult kidney only transplants from deceased donors in the UK in 2018/19**

- 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 a long time 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**

**Disagreement on exact definition of 'highly sensitised' and number of people affected on waiting list**

# Patient perspectives

- Main options for people currently unable to have a transplant are haemodialysis (HD) or peritoneal dialysis (some may have palliative care). Haemodialysis stressful, time consuming, repeated two or typically three 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, difficulty with full time work. Relationship issues, mental health issues. Disadvantages more difficult to manage over time
- Prognosis on dialysis typically poor, can cause bone disease, heart disease. Recurrent infections, run out of access to suitable vessels for HD
- '*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

# 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] (but proportion requiring >1 dose could be higher in target population) |

* Imlifidase was granted a 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

# Clinical and economic evidence summary

| | |
|---|---|
| **Scope comparator** | Established clinical management without imlifidase:<br>• Kidney transplant (may include plasma exchange)<br>• Haemodialysis/haemodiafiltration or peritoneal dialysis |
| **Comparators in company submission and ERG report** | Company: dialysis only, no opportunity to receive transplant<br>ERG: comparator should allow for some modelled patients to receive no dialysis to be in line with clinical practice (some people in highly sensitised population do not receive dialysis, from NHSBT dialysis modality data) |
| **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.<br>54 patients, 25 in company's decision problem cohort (company chose group they designated 'unlikely to be transplanted' to match group they believed was suggested by indication) |
| **Main outcome measures** | Efficacy on crossmatch conversion (ability to create a negative crossmatch test in people who exhibit donor specific antibodies), kidney function (eGFR) (see slide 10 for results) |
| **Model** | Partitioned survival model, 3 health states:<br>dialysis, functioning graft, death |
| **Company ICER** | £33,657/QALY gained (ERG reported), £33,658/QALY gained (company reported) |
| **ICER ranges across plausible scenarios** | £33,657/QALY gained to £87,920/QALY gained. ERG base case £87,920/QALY gained. |

NICE

*eGFR: estimated glomerular filtration rate; NHSBT: NHS Blood and Transplant*

# Clinical perspectives

- Imlifidase innovative. Aim is successful transplant for people who would otherwise have to wait a lot longer for a suitable deceased donor kidney ('successful' = associated with duration and quality of life greater than remaining on waiting list/dialysis)
  - Slightly less successful outcomes compared to non-sensitised deceased donor transplant would still be 'significant treatment response' in this group. People treated with imlifidase would likely see it as better than being on dialysis

- Allocation algorithm prioritises people who are highly sensitised in recognition that there are limited suitable kidneys for them, but still wait longer for a deceased donor kidney (median 5 years compared to 2.5 years, 2016 data)
  - New algorithm implemented 2019 (data on first year of scheme should be ready early 2021), too early to say how much waiting time has reduced but it will never become equal simply by changing allocation
  - Disagreement over whether or not further changes to UK deceased donor Kidney Offering Scheme (KOS) would be needed if imlifidase was recommended
  - Definition of people in 2019 KOS who are 'unlikely to be transplanted' (as per marketing authorisation) needs clarification

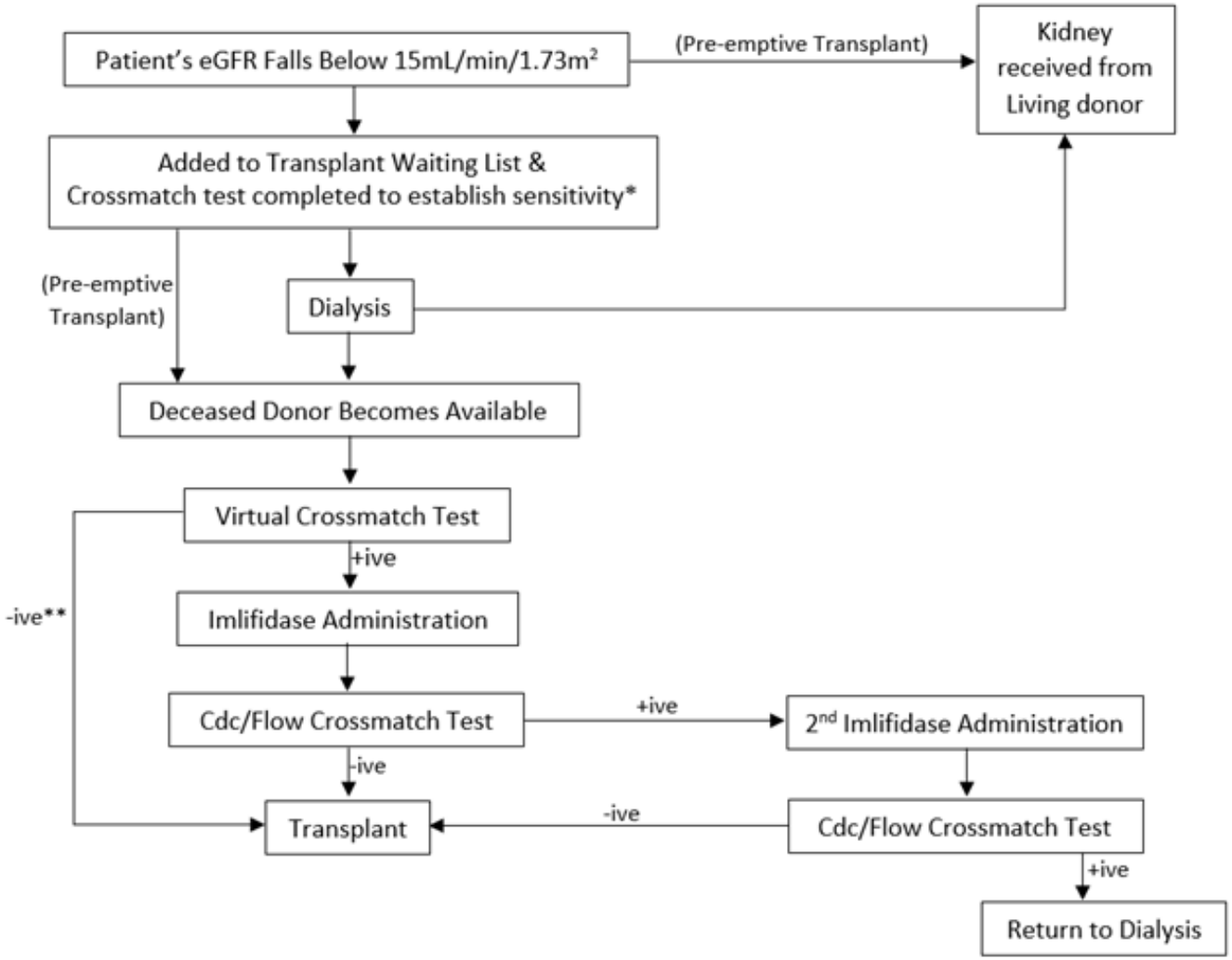


*HLA: human leukocyte antigen; QoL: quality of life*

# Clinical perspectives (continued)

- Success of imlifidase should be measured in long-term outcomes, not just 'transplant achieved' – benefits might be short-term, longer trial follow up results required.
  - 6-month or even 2-year graft survival is short outcome measure for treatment that's known to be associated with return of donor specific antibodies
- Need for concomitant treatments (e.g. intravenous immunoglobulin, rituximab, prophylactic antimicrobials, plasma exchange) remains to be established
- UK living donor national kidney sharing scheme very successful, offers people who are highly sensitised good alternative to deceased donation if they have a living donor
- Grey area over 'unacceptable' mismatch between potential donor and recipient. Variation in level of risk centres will take when there's current/historic circulating donor-specific HLA antibodies, or with HLA antigen mismatches from previous transplants
  - Some centres might be willing to recommend/undertake transplant with enhanced immunomodulation therapy for the person getting the kidney, and/or enhanced surveillance for rejection

# Possible treatment pathway – ERG understanding using clinical opinion and company submission




** Multiple crossmatch tests may be required if on waiting list for an extended period since sensitivity can be increased by events such as pregnancy or transfusion*

*** Clinical opinion is that it is unclear whether a virtual crossmatch would be sufficient in this scenario. It is possible that a crossmatch test would be required irrespective of the outcome of the virtual crossmatch.*

The pathway is uncertain. Integration of imlifidase in clinical practice and the context of the kidney allocation scheme is discussed in issue 2



*eGFR: estimated glomerular filtration rate; Cdc: complement dependent cytotoxicity*

# Clinical efficacy

Combined analyses of patients across all 4 clinical trials of imlifidase, using subgroup of 25 that company considered to match indication in marketing authorisation

**Measure and context**

**CROSSMATCH CONVERSION**

Conversion from positive crossmatch to negative crossmatch is key indicator for compatibility of transplant

**Result**

**IMLIFIDASE**

100% of the 25 people had negative crossmatch after imlifidase treatment

**KIDNEY FUNCTION**

- Estimated Glomerular Filtration Rate (eGFR, measured in mL/min/1.73 $m^2$) of 60 or higher considered 'normal'*
- In UK, just over 15% transplant patients have eGFR <30

**IMLIFIDASE**

- At 6 months:
  - 40% had eGFR ≥60, 50% had 30-59, 10% had <30
  - Kidney function good/satisfactory in all who had functioning kidney and data
- Limited long-term follow-up shows similar function maintained for up to 2 years post-transplant

*Average normal eGFR is 100, eGFR can be seen as percentage of normal kidney function. Values as low as 60 considered normal if there is no other evidence of kidney disease (Kidney Research UK)

# Clinical efficacy (continued)

Measure and context

**Donor-specific antibody (DSA) levels over time**

High total mean fluorescence intensity (MFI) load and/or number of problematic DSAs could lead to graft rejection

Result

**IMLIFIDASE**

MFI of immunodominant antigens of each person in the trials:

| Time | Mean MFI (median) |
|---|---|
| Baseline | [redacted] ([redacted]) |
| Post-treatment | [redacted] ([redacted]) |
| Day 7 post-transplant | [redacted] ([redacted]) |
| Day 14 post-transplant | [redacted] ([redacted]) |
| Day 30 post-transplant | [redacted] ([redacted]) |

- DSA levels remained undetectable for up to 7 days post-transplant before any rebound occurred, allowed transplant to proceed
- Slow steady rebound in DSA values, but in most cases remained below baseline levels

**GRAFT AND PATIENT SURVIVAL**

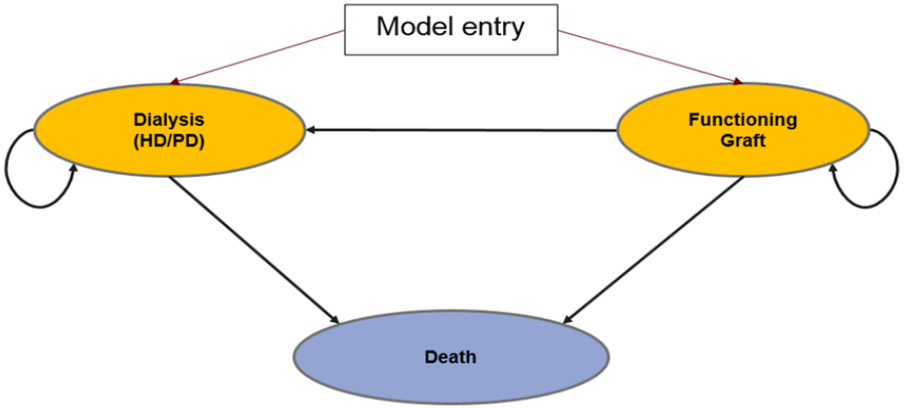
- How long donor kidney (graft) lasts for people in the target population (25) in the trials who had imlifidase then a transplant
- How long people in target population have lived after having imlifidase then a transplant

**IMLIFIDASE**

- At end of trial periods (6 months), all patients were alive, 24/25 (96.0%) had functioning graft
- Long-term follow-up: death-censored graft survival [redacted] at 2 years, overall patient survival [redacted] at 2 years (skewed by 3 deaths in small population, none considered related to imlifidase/kidney malfunction)

# Company model

- Standard, cohort-simulation, 3 state Markov model (dialysis [haemodialysis or peritoneal dialysis], functioning graft, death)
- Lifetime time horizon with a 6-month cycle length, half-cycle correction applied
- Variable transition probabilities between each state
- Published utilities used from meta-analysis
- iBox extrapolation of trial data for long-term graft loss rates after imlifidase




- Functioning graft state is entry point into model for people treated with imlifidase - so transitions out this state based on available clinical data for imlifidase.
- From functioning graft state, people can transition to either dialysis (modelled to occur when graft lost) or death state. Transitions modelled using graft survival and patient survival data, vary based on length of time since transplant
- Within dialysis state, people can transition to death state. Modelled as additional age-based relative risk of death - based on data from UK Renal Registry, combined with background mortality from UK life tables (calculated based on age and gender of modelled population)

Originally assumed:

- 0% of people in comparator arm get transplant without imlifidase
- 100% of people treated with imlifidase go on to have a transplant

# Some agreements possible at technical engagement

- **Key issues 1-7 not resolved,** but company accepted error corrections ERG made, and some of ERG's preferred assumptions:
  - Caregiver disutility source, disutility applied for 90% of modelled patients on haemodialysis
  - Included costs of DSA test annually for transplant patients in model and at time of graft loss, cost of one crossmatch test following each full dose of imlifidase
  - Used average patient weight from trials

- Company also made amendments to base case to better reflect ERG's critiques (but with different values), discussed in key issue 6 as disagreement remains over parameters:
  - Use 97.9% (45/46) as proportion of all people treated with imlifidase who have subsequent transplant (100% in company's original base case) i.e. changed to intention-to-treat perspective
  - Allow 1.0% of people in comparator arm to have a transplant (0% in company's original base case), i.e. some people in comparator arm have transplant without imlifidase

- ERG views on issues 1-7 remain unchanged after technical engagement

| Outstanding issues unresolved post technical engagement | Status | Impact | Slide |
|---|---|---|---|
| **Issue 2:** Placement of imlifidase in the UK treatment pathway | For discussion | | 15-16 |
| **Issue 3:** Generalisability of the evidence to NHS contexts | For discussion | | 17-18 |
| **Issue 4:** Interpretation of treatment outcomes following transplant | For discussion | | 19-20 |
| **Issue 5:** Comprehensiveness of the clinical evidence base | For discussion | | 21-22 |
| **Issue 6:** Comparators in the economic model | For discussion | | 23-25 |
| **Issue 7:** Quality of life data used in the economic model | For discussion | | 26-27 |
| **Issue 1*:** Relevance of comparators and methodological uncertainty | For discussion | | 28-29 |

Model driver

Unknown impact

Small/Moderate impact

NICE

*NB, issues not in same order in slides as during technical engagement

# Issue 2: Placement of imlifidase in the UK treatment pathway

**Background**

- Algorithm used by KOS altered in 2019 to give greater priority to people who are sensitised. Not known whether it would be appropriate to adjust KOS algorithm to ensure equality of access if imlifidase were to be introduced
- ERG: uncertainty about impact of imlifidase on treatment pathway and KOS, and further input needed from stakeholders would be useful (engagement responses highlighted uncertainty)

**Company comments**

- Considerations of changes to KOS are beyond scope of a NICE appraisal, therefore beyond remit of this appraisal
- When imlifidase is used in line with its licence (for small number of patients who do not benefit from KOS), there should be no necessity to alter KOS in the short term to accommodate its use (view supported by UK clinical experts consulted)
- Practicalities of use of imlifidase and associated treatment protocols still need to be fully decided within a UK setting. “UK unified approach” (potentially including use and pre-identification of suitable candidates, immunologic risk profile, pre- and post-transplant immunosuppression and safety monitoring based on trial designs as a framework) developed by a working group of UK experts may be a suitable way forward.



*KOS: Kidney Offering Scheme*

# Issue 2: Placement of imlifidase in the UK treatment pathway

**Stakeholder comments**

- Already evidence that algorithm change is delivering more transplants to Tier A patients (cRF=100, >7 years wait or matchability score of 10). Not sure that KOS would need to be altered if imlifidase were to be used since individual centres would remove unacceptable antigens resulting in allocation. Would need to be some control and agreement on when this should take place
- Anticipate following pathway: 1) Identification of appropriate wait-listed patients 2) Identify those HLA specificities to which the patient has antibodies likely removed by imlifidase 3) Those specificities would be 'de-listed' as unacceptable on UK waiting list, allowing offer of a kidney with one or more previously unacceptable HLA types 4) By removing some unacceptable HLA specificities the patient's cRF would necessarily reduce
  - Point 4 is the only point relevant to the management of the waiting list – NHSBT would need to take a position as to whether patient remained listed with original cRF or modified cRF. KOS itself would not need modification
- Need clinical consensus on various stages of the pathway, and identification and clinical use in limited transplant centres with experience of managing HLA-incompatible kidney transplantation (before wider adoption). Changes in UK deceased donor kidney allocation scheme would be required to incorporate imlifidase into treatment pathway

**Are there any potential changes to the treatment pathway and current allocation scheme that need to be considered in decision making?**



*cRF: calculated reaction frequency; NHSBT: NHS Blood and Transplant*

# Issue 3: Generalisability of the evidence to NHS contexts

**Background and ERG views**

- Clinical evidence solely from 4 single-arm early phase studies with varying trial protocols (25 participants in decision problem population). Several outcomes could be biased from confounding, distribution of effect modifiers. Relative treatment effects can't be estimated from trials, company's effectiveness relies on implicit assumption that without imlifidase, particular outcomes would not have been observed
- No studies in UK - disease mechanism may be consistent across centres/geographical areas, but national/local transplant protocols have considerable impact on pathway, clinical and cost effectiveness. No published data for demographics and outcomes of this group that would be seen in NHS without use of imlifidase
- **ERG** - issues considerably complicate ability to generalise effects to UK population, especially given that company's economic model relies in its base case on this implicit assumption. Matched comparison would have increased confidence in analysis

**Company comments**

- Aware there are differences between kidney allocation/priority schemes between countries, differences in treatment protocols. Underlying biology consistent so generalisability of data across countries can be assumed
- Confident that trial evidence generalisable to NHS. Received UK clinical expert support, and of generalisability of clinical evidence to NHS context

# Issue 3: Generalisability of the evidence to NHS contexts

**Company comments (continued)**

- ERG states that matched comparison would be desirable additional evidence. Analysis not conducted, Hansa has not identified literature to inform matched comparison within indicated population - due to indication being new, very small population, not been extensively studied

**Stakeholder comments**

- Essential point in some ways. Imlifidase would be for small numbers on waiting list – similar to those in small trials. Would be impossible to conduct an RCT in this patient group, and hard to generalise use for this indication to wider NHS. Use specifically targeted at group where existing NHS treatment (a successful transplant) effectively denied
- People treated in trials so far in USA and continental Europe. Principles should be applicable to similar healthcare system in UK
- KOS UK-specific, makes comparisons difficult. UK living donor kidney sharing scheme very successful, offers people who are highly sensitised good alternative to deceased donation if they have living donor. Would be ethical to conduct RCT where control group gets standard care of waiting for suitable transplant from KOS - enable meaningful comparison of patient survival, quality of life, adverse events, cost

**Technical team**

Impact of lack of generalisability on ICER couldn't be quantified

**Should a matched comparison be carried out to strengthen the clinical evidence?**

**Is evidence in UK patients/NHS context needed for decision making?**



*RCT: randomised control trial*

# Issue 4: Interpretation of treatment outcomes following transplant

**ERG views**

- Lack of more rigorous, matched evidence is limitation, interpretation of transplant outcomes uncertain
  - company did not present systematically identified evidence base to make naïve comparisons with trial outcomes, would have helped interpretation of clinical effect (e.g. if rejection rate post-transplant comparable with non-sensitised deceased donor transplants)
- Transplant outcomes following imlifidase based on those reported in included trials, extrapolated using iBox. Unclear if company's studies are in more/less favourable population, clinical data validity in model unclear
- Potential impact on ICER unclear without further evidence

**Company comments**

- Developed for orphan indication under EMA PRIME scheme, granted a CMA in orphan indication, limited data available
- All available evidence presented to NICE, further data collection on post-transplant outcomes ongoing, mandated within CMA
- Additional data from trial outcomes used as input to robust and validated graft survival prediction algorithm (iBox, developed by Paris Transplant Group)
- Rare at launch for studies on orphan product to have this type of advanced data and such a robust prediction of long-term efficacy – prediction made through iBox ensures more robust economic modelling with less uncertainty for imlifidase



*CMA: conditional marketing authorisation*

# Issue 4: Interpretation of treatment outcomes following transplant

**Stakeholder comments**

- Agree with ERG that extrapolating long-term outcomes is difficult from small short-term clinical experience currently available. Agree with company that using iBox methodology is reasonable and sensible, that acceptable long-term (5 and 10 year) outcomes are realistic. Much depends on patient selection
- Practical option 'Commissioning through Evaluation' approach available within NHSE specialised services - controlled introduction of imlifidase, harness strengths of transplantation in UK – national service with established central listing and organ allocation organisation, robust national data collection, excellent pedigree in national clinical trials
- Available data too short term. Data from studies (n=25) very small in context of scope, national registry of outcome and review should be established to capture immediate and long-term data
- Treatment regimen after imlifidase has significantly intensified immunosuppression (alemtuzumab, rituximab, IvIGs in addition to triple therapy). Concerns over long term safety, studies have relatively short follow up, antibody-mediated rejection (AMR) very expensive to treat

**Technical team**

Without further evidence, potential impact of this issue on ICER is unclear

**Is the clinical efficacy evidence presented by the company valid and sufficient for decision making?**



*IvIGs: intravenous immunoglobulins, NHSE: NHS England*

# Issue 5: Comprehensiveness of the clinical evidence base

**Background and ERG views**

- Outcome data should follow gold standards for reporting of clinical and safety evidence in a NICE submission
- **ERG** thought evidence in CS from company's clinical evidence review poorly reported, significant gaps that limited understanding of clinical and safety outcomes following imlifidase.
  - Not all outcomes evaluated in each trial, but where outcomes evaluated these were not always reported (for individual trials as well as for pooled analyses by company).
  - Timing of measurement often unclear, continuous data frequently reported without variance data
- Significant uncertainty on efficacy and safety in target population. **ERG** concerned over poor reporting of crossmatch conversion data (primary outcome for trials), type and consequences of AMR episodes
  - Wanted to see all scoped outcomes measured in trials reported for all included studies and relevant pooled analyses

**Company**

- Target population same as licensed population. EMA found data presented for this group sufficient to demonstrate safety and efficacy of imlifidase and allowed granting of CMA.
- Summary of clinical efficacy produced by ERG (Appendix B to its report) provides full and accurate picture of available clinical data within most relevant patient population



*AMR: antibody-mediated rejection*

# Issue 5: Comprehensiveness of the clinical evidence base

**Company (continued)**

- Provided some clarity on timing of crossmatch tests and related SmPC wording, at technical engagement
- All available data related to scoped outcomes have been presented to NICE and no additional data are available in that regard

**Stakeholder comments**

- Evidence base consists of early phase uncontrolled trials of small numbers of subjects with relatively short follow up, significant limitation. Longer term data (renal function, proteinuria and protocol biopsy data) not clear
- Clinical data is limited, short term, in heterogenous subjects and not treated according to existing UK practice. UK trial in selected centres of excellence is advised
- Several stakeholders indicated their response for issue 5 was in line with their response for issue 4

**ERG view at technical engagement**

Disappointed that company did not use opportunity at technical engagement to provide the clinical effectiveness data in a way that would have given greater confidence in the findings. As a consequence, ERG cannot fully validate clinical effectiveness estimates

**Technical team**

Uncertainty over efficacy leads to lack of confidence in company's cost-effectiveness estimates

**Should any of the clinical effectiveness data be provided in a different way to enable validation of clinical effectiveness estimates?**

# **Issue 6:** Comparators in the economic model

**Background**

- Company model used post-hoc view i.e. given a person got a transplant, versus remaining on dialysis.
  - Not all people who receive imlifidase go on to have a transplant, and not all people who are untreated with imlifidase are on dialysis (as per NHSBT modality data) or don't have a transplant – particularly in light of revised KOS, greater priority given to people who are highly sensitised
- Company's original base case:
  - Proportion of people in comparator arm having transplant without imlifidase assumed 0% over lifetime horizon
  - 100% of people who had imlifidase go on to have transplant. Unrepresentative of reality, small number of people may not have a transplant following imlifidase (seen in studies)

- **ERG** thought company's post-hoc view did not match scope (compares imlifidase versus clinical management without imlifidase), **preferred intention-to-treat approach**
- **ERG** preferred assumption is **31.44% of people on dialysis having a transplant** (to reflect that some people on dialysis who are highly sensitised would have a transplant without imlifidase), derived from NHSBT data (instead of company's 0%)
  - **Best proxy so far, but recognise limitations** of this assumption, with **exact rate likely to be determined by characteristics of patient population** who would be treated - **population remains unclear and undefined**
- **ERG**'s base case used trial data: 2/54 participants discontinued imlifidase before transplant (**96.3% having transplant in imlifidase arm** in ERG base case)
  - 1/52 remaining participants did not have negative FACS crossmatch (outcome of trial) but received subsequent transplant anyway. ERG presented scenario where proportion of people having transplant in imlifidase arm is informed by those who had full dose multiplied by those who achieved negative crossmatch (94.4% having transplant in imlifidase arm)

*FACS: fluorescence-activated cell sorting*

# Issue 6: Comparators in the economic model

**Company**

- Relevant comparison is imlifidase treated patients versus those same patients receiving clinical management without imlifidase – which should be dialysis
  - Intended as treatment to allow transplant in people who have exhausted all other options and remain unlikely to have transplant. Unlikely to include people who are pre-dialysis and being pre-emptively transplanted, as they are at start of renal replacement therapy, likely have other options
  - Company's UK clinical experts thought treatment without imlifidase would be dialysis for all, with potentially only very small minority not on dialysis initially (would start within 6 months of joining waiting list)
- Accept ERG point that unlikely to be transplanted does not mean there's no chance of transplant
  - By definition, these patients are unlikely to be transplanted so this value would be very low (sought UK clinical expert advice). Do not have additional data for this estimation currently, but better clinical definition of group may allow more appropriate data to be gathered from NHSBT
  - **Used 1% of people in comparator arm having transplant** in updated company base case (instead of 0%)
- Revised original estimate of **proportion of imlifidase patients assumed to have a transplant** to **97.9%** (45/46 patients in trials excluding 13-HMedIdeS-02 study successfully receiving a transplant).
  - Participant who did not have full crossmatch conversion had borderline flow crossmatch and negative virtual crossmatch following imlifidase. Could not be considered full crossmatch conversion, but result judged not clinically significant within time-critical situation, transplant successfully carried out

# Issue 6: Comparators in the economic model

**ERG views in light of technical engagement responses**

- Disagree with exclusion of 13-HMedIdeS-02 study - key trial outcomes didn't include transplantation but evidence remains that 1 participant was discontinued due to adverse events. With limited patient numbers, ERG's view is unchanged, make no adjustment to ERG's preferred base case assumptions
- Using other ERG preferred assumptions but with 1% rate of transplant in people in comparator arm proposed by company, or 4% rate suggested by clinical responses to technical engagement (which ERG believe to be annual rate, converted to 7.84% lifetime rate), ICER remains over £50,000/QALY

**Stakeholder comments**

- Could be resolved by company only charging for drug when transplant proceeded
- Economic model makes assumptions about long-term survival of the kidney transplant that are not supported by long-term data yet
- Majority of people who are highly sensitized wait for many years for offer of compatible kidney, inevitably become dialysis dependent
- Significant proportion of people who are highly sensitised may be either pre-emptive with some native kidney function or failing transplant
- Company consider that it would be unethical to perform an RCT because there is no safe alternative to be comparator. → 1 stakeholder disagreed and believed it would be ethical to conduct a RCT where control group receives standard care of waiting for a suitable transplant from KOS. Would enable meaningful comparison of patient survival, quality of life, adverse events and cost
- One of the other comparators and even a small pilot study in UK would be useful (imlifidase versus maximal delisting strategies in context of 2019 KOS)

**Which values should be used for:**

**a) proportion of people treated with imlifidase who have a transplant?**
**b) proportion of people in comparator arm who have a transplant without imlifidase?**

# Issue 7: Quality of life data used in the economic model

**Background and ERG views**

- No quality of life (QoL) data collected in company clinical studies, with literature data from pre-2005 used in economic model which has methodological issues
- **ERG** identified a systematic review of utility values which had been published after the company submission date (Cooper et al. 2020). Considered this source a more relevant reference but uncertainty around impact of imlifidase on QoL uncertain - data collection using Patient Reported Outcomes from people who have received imlifidase and undergone a transplant would be useful

**Company comments**

- ERG values stated to use longitudinal data reported within Cooper source - believe these are derived from single publication by Ortega T et al. 2007 (Spanish population). Exact characteristics of study population unclear, appears to be general transplant population. Raises questions around applicability of data to UK and population of interest:
  - Spain has high availability of deceased donor organs, people get transplant after 8 months on average (median 633 days for all people on UK waitlist)
  - Study represents general pre-transplant population, likely includes some pre-emptively transplanted people who are pre-dialysis/have been on dialysis for limited time periods. Utilities likely substantially higher for this group than for people who have been on dialysis for many years (like for imlifidase population – people in trials on dialysis for over seven years on average)

# Issue 7: Quality of life data used in the economic model

**Company comments (continued)**

- Dialysis-specific utilities more representative of appraisal population and modelled population across time horizon – publication used for Hansa base case contains most appropriate available data (meta-analysis focussed on general dialysis population, broad mix including people on long-term dialysis)
- Model does not include utility impact from long-term dialysis and removal from transplant list. Mental health issues (e.g. depression, loss of hope when transplant no longer an option) likely to have significant utility impact, but hasn't been possible to source data to include these factors. Would likely decrease QALYs in comparator group and reduce ICER for imlifidase
- QoL data being collected in long-term follow-up study of imlifidase trials (17-HMedIdeS-14), similar data being collected in post-approval studies. No QoL data currently available for people treated with imlifidase

**Stakeholder comments**

- Data on this is very limited/unavailable

**Should the model use the company's base case utility values, or those sourced from the Cooper et al. systematic review of utility values?**

# Issue 1: Relevance of comparators and methodological uncertainty

**ERG**

- Finite number of donor kidneys are available, did scenario analysis where transplant is provided to people who are not considered 'highly-sensitised' so don't require imlifidase – 'opportunity cost' of donor kidney
- Giving a kidney where imlifidase needed vs where imlifidase not needed (£30k threshold):
  - imlifidase dominated
  - net benefit [redacted] (a loss)
  - net health benefit [redacted] QALYs (a loss)

**ERG at technical engagement**
Reiterated that approach not used in ERG base case, question of scope is for committee to decide

**Company comments**

- Major advantage of imlifidase is greater equality of access to kidney transplant ('equity in provision of transplant')
  - licensed (and target) population have significantly increased wait times for transplant, many may never have suitable donor organ offer
- 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 primary 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

NICE

*KOS: Kidney Offering Scheme*

# Issue 1: Relevance of comparators and methodological uncertainty

**Stakeholder comments**

- By transplanting using imlifidase then another person would not be transplanted, but this is the case for every deceased donor or living donor kidney transplanted. Speculating on impact on whole waiting list impossible. Majority on list are pre-dialysis and non-sensitised, very likely to be transplanted with different kidney in short time with negligible additional cost
- Any organ used with imlifidase could be used for someone else in a much cheaper fashion, with better outcomes and equal dialysis avoidance-related savings. May seem desirable from individual patient perspective but difficult to see any cost savings for overall healthcare system
- Health economic modelling must take into account cost to healthcare system as a whole and not be patient centred, especially when supply of organs is insufficient for need in UK

**Technical team**

- Any kidneys not received by people having imlifidase would be received by others on list; imlifidase will not increase number of kidneys available to transplant. To reflect all costs and benefits, might need to include opportunity (health) cost of kidneys, as finite resource in system.
  - But existing inequalities would need to be considered (slide 31), may not be a case of deciding based on net health benefit or cost-effectiveness alone
- Net health benefit analysis shows potential for imlifidase to lead to overall loss of [redacted] QALYs per deceased donor kidney, compared to theoretical maximum that could be gained from each kidney (giving it to someone who doesn't need imlifidase)

**Should the appraisal consider the costs and benefits of kidney transplant in those not eligible to have imlifidase?**

NICE

*QALY: quality-adjusted life year*

# Additional issues/uncertainties raised

| Issue | Why issue is important | Impact on ICER |
|---|---|---|
| Clinical experience with imlifidase has used induction immunosuppression with agents including anti-CD20 antibody, alemtuzumab, and equine anti-thymocyte globulin | None of these are currently recommended by NICE or commissioned by NHSE. Commissioning of imlifidase would require limited commissioning of these agents. Extent to which they're used alongside imlifidase unknown | Costs should be included in the analysis – likely to increase the ICER |
| ERG document refers to frequency of HLA antibody screening – with testing frequency as low as once yearly, and perhaps monthly in imlifidase-treated patients. Clinical reality in UK is different | For people who are highly sensitized, HLA antibody screening will be both frequent and equivalent for both those receiving a compatible kidney (to ensure that they do not develop new DSA), and for imlifidase-treated patients (to monitor DSA rebound) | Additional testing costs in imlifidase arm of model would increase ICER |
| People who are 'unlikely to be transplanted' in new 2019 kidney allocation scheme requires further clarification - data on one year of the scheme should be ready by February 2021 | Early data suggest small increase in transplantation in people with cRF of 100% compared to 2006 scheme (4% versus 2%) with greater benefit for other category, cRF 85-99%, 19% versus 11%. But difficult to define this population up-front, can only define it because of something that hasn't happened (a kidney transplant). Some people with a cRF of 85-99%, or even CRF of 100%, are going to be transplantable without imlifidase | Unknown |

# Equalities

**Stakeholder views during appraisal**

- No equality issues when considering this treatment as such but application of technology and individual centre practices may create equality issue when implementing this as evidenced by wide difference in waiting times across centres in UK. Issues are likely to amplify with current practise with different risk aversion/behaviour of individual centres
- Equality of access in transplantation is very important but I don't think availability of this medicine creates any new issues in that respect

**Potential equality considerations raised during scoping**

- Imlifidase may offer people who are highly sensitised in minority ethnic groups, who already have difficulty accessing a matched donor kidney, a desensitisation option to enable access to a deceased donor kidney. These people with protected characteristics could gain access to a donor kidney sooner so could have better outcomes once transplanted. Limited trial evidence in BAME population. Are people in minority ethnic groups disadvantaged through being highly sensitised (i.e. a higher rate), or because available donor pool of suitable kidneys is smaller due to being in a minority ethnic group?
- One of most common causes for a person to be highly sensitised is previous pregnancy. According to British Transplant Society guidelines, pregnancy-induced sensitisation is major reported risk factor for early AMR in donor specific HLA antibody incompatibility transplantation, especially where donor is patient's child or father of a child with the patient (so people in this situation may be more likely to require an organ from a deceased donor)
  - For most sensitised (with positive crossmatch through Complement Dependent Cytotoxic [CDC] test), see very different 10-year survival results by sex – approximately 67-68% (males) versus 15% (females)
  - Survival probability of CDC positive males significantly higher than for CDC positive females. May be related to graft survival

*AMR: antibody-mediated rejection; BAME: Black, Asian and minority ethnic*

# Cost effectiveness results

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| **Company base case (corrected, and after their technical engagement changes):** | | | |
| 1% lifetime transplant rate in comparator arm; 97.9% of people who had imlifidase to receive a subsequent transplant | [redacted] | [redacted] | 33,657 |
| Issue 6: | | | |
| 7.84% lifetime transplant rate in comparator arm | [redacted] | [redacted] | 38,343 |
| 31.44% lifetime transplant rate in comparator (ERG preference) | [redacted] | [redacted] | 61,927 |
| 96.3% of people who had imlifidase to receive a subsequent transplant (ERG preference) | [redacted] | [redacted] | 34,710 |
| Issue 7: | | | |
| Utility source – Cooper et al. (2020) | [redacted] | [redacted] | 41,829 |
| **ERG base case (after technical engagement):** | | | |
| 31.44% lifetime transplant rate in comparator; NHSBT proportions of dialysis modality applied (including not on dialysis, haemodialysis, peritoneal dialysis); 96.3% of people who had imlifidase to receive a subsequent transplant; utility source Cooper et al. (2020) | [redacted] | [redacted] | 87,920 |
| **Scenario with lower lifetime transplant rate in comparator arm:** | | | |
| Other assumptions as in ERG base case, but with 7.84% lifetime transplant rate in comparator arm | [redacted] | [redacted] | 57,240 |

# Key issues

**Issue 2:** Are there any potential changes to the treatment pathway and current allocation scheme that need to be considered in decision making?

**Issue 3:** Should a matched comparison be carried out to strengthen the clinical evidence? Is evidence in UK patients/NHS context needed for decision making?

**Issue 4:** Is the clinical efficacy evidence presented by the company valid and sufficient for decision making?

**Issue 5:** Should any of the clinical effectiveness data be provided in a different way to enable validation of clinical effectiveness estimates?

**Issue 6:** Which values should be used for:
a) proportion of people treated with imlifidase who have a transplant?
b) proportion of people in comparator arm who have a transplant without imlifidase?

**Issue 7:** Should the model use the company's base case utility values, or those sourced from the Cooper et al. systematic review of utility values?

**Issue 1*:** Should the appraisal consider the costs and benefits of kidney transplant in those not eligible to have imlifidase?



**NB, issues not in same order in slides as during technical engagement*