Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1732 – Imlifidase in the desensitisation treatment of highly sensitised adult kidney transplant patients with a positive crossmatch against an available deceased donor or living donor, who are unlikely to be transplanted under current kidney allocation systems

Applicant: **Hansa Biopharma Australia**

Date of MSAC consideration: **27 July 2023**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting the use of imlifidase in the desensitisation treatment of highly sensitised (HS) adult kidney transplant patients with a positive crossmatch against an available deceased donor (DD) or living donor (LD) who are unlikely to be transplanted under current kidney allocation systems was received by the Department of Health from Hansa Biopharma Australia.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of imlifidase as desensitisation treatment of highly sensitised (HS) adult kidney transplant patients with a positive crossmatch against an available deceased donor (DD) or living donor (LD) who are unlikely to be transplanted under current kidney allocation systems, with a calculated panel-reactive antibody (cPRA) of 95% or higher.

MSAC noted the very positive impact of the recent change in the algorithm for the allocation of deceased donor kidneys on access to kidney transplantation for patients with a cPRA level from 95% to less than 99%, but noted a clinical need for equity of access in the subgroup of patients with a cPRA level of 99% or more. MSAC did not accept that imlifidase is comparatively safe, effective or cost-effective in the proposed target population (cPRA 95% or higher), noting a number of issues in relation to the clinical place of therapy, clinical data, cost and economics. MSAC considered that the clinical need only remains in a subset of patients - the higher immunological risk group (99% or more). There are alternative treatments available for both deceased and living donor recipients that need to be considered. MSAC noted the clinical data are of low confidence given the design and conduct issues (small sample size, heterogeneous immunological risk, single arm, and short term), and that the underlying processes for graft rejection remain, being only mitigated for up to one week. There are also complex implementation issues and a requirement for more immunological tests in the acute setting than would be used in routine clinical practice. MSAC noted there are displacement issues in the setting of deceased donor recipients with patients of lower immunological risk, who would have

received a kidney, being replaced by a higher immunological risk recipient (noting that deceased donor kidneys are a scarce resource).

MSAC did consider that there was a clinical need for therapies like imlifidase in the very high immunological risk setting, for a small group of patients who would otherwise not be transplanted or receive a transplant after a considerable period of waiting (cPRA 99% or above) in whom alternative therapies were not effective or possible. Further consultation is required to ascertain the clinical place of therapy, with separate consideration of deceased donor and living donor kidney recipients in light of other potential comparators, and reconsideration of the proposed price.

Consumer summary

This is an application from Hansa Biopharma Australia requesting National Health Reform Agreement (NHRA) funding of imlifidase as a desensitisation treatment of highly sensitised adult kidney transplant patients with a positive crossmatch against an available deceased or living donor who are unlikely to be transplanted under current kidney allocation systems.

End-stage kidney disease is defined by partial or complete failure of kidney function. Patients with end-stage kidney disease need regular dialysis or a kidney transplant to survive. A kidney transplant gives patients a greater chance of survival and a better quality of life than remaining on dialysis.

Around one-third of people waiting for a kidney transplant have donor-specific antibodies against human leukocyte antigens, which means that they have a higher chance of rejecting a donor kidney. These people are classified as “highly sensitised” and include groups such as women who have previously been pregnant and people who have already had a transplant.

Imlifidase is a “desensitisation” treatment that tries to prevent the body from rejecting a newly transplanted kidney. This treatment is used before transplantation in people who are considered “highly sensitised” based on a positive crossmatch test. A positive crossmatch is where a high level of antibodies (measured as calculated panel reactive antibody values, or cPRA) in the person receiving the transplant bind to the cells of the donor (or the donor’s kidney) and destroy them. Imlifidase converts people from crossmatch positive to negative, which reduces the likelihood of the patient’s body rejecting the donated kidney for about 1 week (the peak period for a very serious form of rejection, called hyper-acute rejection).

MSAC acknowledged that imlifidase treatment may provide some benefit to patients who would otherwise be less likely to receive a donor kidney, especially people with cPRA greater than or equal to 99%. However, there were several issues that meant that MSAC could not support funding. These included that the proposed population (cPRA≥95%) included people who already have a very high rate of transplantation due to receiving priority under current kidney allocation algorithms (those with a cPRA from 95% to below 99%); the effect of providing kidneys to people at high risk of rejection on increasing the waiting time for others on the waitlist who are not in the proposed population and who would be likely to have better clinical outcomes with a donor kidney was not considered (as kidneys are in short supply); other treatments in clinical use were not considered; and implementation costs were not included in the economic model (such as further immunological testing and increased staffing requirements). These issues meant that MSAC was uncertain that imlifidase was safer or more effective than the proposed comparator of continuing to receive dialysis or relative to other potential comparators, nor that it was good value for money.

MSAC’s advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support funding imlifidase as a desensitisation treatment of highly sensitised adult kidney transplant patients with a positive crossmatch against a deceased or living donor.

Consumer summary
MSAC acknowledged that imlifidase may provide some benefit to a specific group of patients. However, there were several issues with the submission that meant that MSAC was uncertain that imlifidase was safer or more effective than the proposed comparator of continuing to receive dialysis or relative to other potential comparators, nor that it was good value for money. MSAC advised that any resubmission would be considered by the Evaluation Sub-committee (ESC) before coming back to MSAC.

3. Summary of consideration and rationale for MSAC's advice

Applicant hearing

The applicant was granted a hearing during which they presented information to MSAC on imlifidase including the current status of its regulatory approvals, its clinical role, the applicant's view of its cost effectiveness and implementation issues.

The applicant noted that the Therapeutic Goods Administration (TGA) had made a decision to provisionally register Idefirix (imlifidase). This provisional approval was for the desensitisation treatment of highly sensitised adult kidney transplant candidates prior to kidney transplantation from a donor against whom there is a positive cross-match. The indication wording also included a statement that the use of Idefirix should be reserved for patients who are otherwise unlikely to receive a kidney transplant. Idefirix (imlifidase) was included in the ARTG on 10 July 2023, and on this date the provisional registration period of 2 years commenced. The applicant noted that the European Union (EU) had also granted conditional Marketing Authorisation in August 2020 and reimbursed access had been achieved across a number of European markets.

An Australian clinician supporting the applicant stated that approximately 21% of patients on the Australian kidney waitlist were HS (defined as those with a calculated panel reactive antibody [cPRA] value of 95% or more) and that these patients were difficult to match with an available kidney and therefore remained waiting on chronic dialysis, which has significant impacts on healthcare costs, morbidity, mortality and quality of life (QoL). Transplantation confers substantial survival and QoL advantages compared with dialysis. Causes of sensitisation include previous transplantation, pregnancy and blood transfusion. It was noted that recent amendments to the Australian prioritisation algorithm (introduced May 2021) meant that HS patients (cPRA ≥95%) are prioritised after being on the transplantation waitlist for one year.

The clinician stated that imlifidase had demonstrated crossmatch conversion in all patients dosed per the proposed indication, regardless of donor or recipient characteristics.

MSAC questioned the clinician about whether patients with a cPRA of 99% or more could be classified as having the highest clinical need based on waiting list statistics given the recent amendments to the prioritisation algorithm which gave priority to patients with cPRA ≥95%. The clinician estimated that at least [redacted] people with cPRA of 99% or more would receive imlifidase each year, but admitted that this was difficult to estimate. The clinician agreed that patients with cPRA of 99% or more had the greatest clinical need, noting the impact of the recent change in the algorithm and the favourable impact upon those with a cPRA from 95% to less than 99%.

The applicant stated that only one out of the five model scenarios adjusting for key uncertainties identified by ESC resulted in an ICER greater than [redacted], and this was the respecified base-case ICER of [redacted]/QALY gained which excluded dialysis cost savings for the HS attributed to imlifidase because this also came with displacement effects for the non-HS who would

correspondingly experience delays in accessing a kidney. The applicant did not agree with the validity of this respecified base case, as such a scenario implied that it would not ever be cost effective to transplant older and diabetic patients. The applicant noted that none of the scenarios analysed in the ADAR incorporated the additional benefits of equity of access to transplants to HS patients who are unlikely to be transplanted and this had to be taken into account when interpreting the ICER values. The applicant reiterated that one patient treated with imlifidase could lead to multiple patients coming off dialysis (through an organ donation chain). The applicant endorsed an ICER of $[redacted] per QALY gained as the most appropriate scenario for consideration and requested that MSAC focus on this ICER because it symmetrically ignored both the contentious 'spillover' benefits from closing linked kidney chains and the 'spillover' costs of displacing non-HS patients.

On implementation issues, the applicant stated that it was working with leading Australian transplant clinicians, many being members of the Renal Transplant Advisory Committee (RTAC) of the Transplantation Society of Australia and New Zealand (TSANZ), on an Australian-specific protocol around patient eligibility criteria, logistical considerations and post-transplant management. The applicant also stated that it welcomes a discussion regarding commercial agreement terms, appropriate to the clinical context of imlifidase, to ensure that Australian patients can secure national funding.

MSAC discussion

MSAC noted that this application from Hansa Biopharma Australia was requesting funding for the use of imlifidase in the desensitisation treatment of highly sensitised (HS) adult kidney transplant patients with a positive crossmatch against an available deceased donor (DD) or living donor (LD) who are unlikely to be transplanted under current kidney allocation systems. Funding requested is via the National Health Reform Agreement (NHRA) Addendum for highly specialised therapies.

MSAC noted that donor kidneys, from both LDs and DDs, are a fixed and scarce resource – in Australia in 2021, there were more than 15,000 people receiving dialysis, around 1,300 people on the kidney transplant waitlist and 857 kidneys transplanted.

MSAC noted that kidney transplantation is carefully managed through a complex two-step process (listing and transplant) that occurs at national and state levels, which includes an algorithm based on age, time on dialysis and immunological match (blood group and human leukocyte antigens [HLAs], which may present significant immunological barriers to transplantation).

MSAC noted the claim of the pre-MSAC response that access to kidney transplantation for HS patients is a major source of inequity, especially for women who have been pregnant, First Nations people and those who have received a kidney previously.

MSAC noted the claim that there was an unmet clinical need for HS patients to be able to receive donor kidneys and move off dialysis, and that imlifidase treatment is the only option that can increase equity of access for HS patients who may otherwise remain on dialysis for a long time waiting for a suitable donor, despite being prioritised. However, MSAC considered that clinical need was low for patients with cPRA ranging from 95% to less than 99%; based on data from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA). Following the Australian prioritisation algorithm changes, this group have the highest rate of transplantation (71% in May 2021) of any group, and there are few of these patients on the transplantation waitlist (*n* = 58, or 4% of the total waitlist in 2021). MSAC also noted that the applicant had estimated that, in the absence of imlifidase, 96% of patients with cPRA ≥95% had <1% compatible donors in the Eurotransplant database, and had argued that Australian data would be similar. However, MSAC

noted that the commentary disagreed with this assumption, as 43.6% of patients on the Australian DD waitlist with cPRA 95–98% are transplanted in the first year.

MSAC considered that the clinical need was highest for patients with cPRA of 99% or more, as they are transplanted at a lower rate. In 2021, approximately 11% (*n* = 153) of the 1,338 people on the kidney transplant waitlist had cPRA of 99% or more, and 140 of those had been on the waitlist for two or more years. MSAC noted that some of this group received desensitisation protocols (IVIG, rituximab, plasma exchange) for LD and DD kidney transplantation and to enable patients to participate in the ANZ Kidney Exchange with Living Related Donors (LRDs). MSAC considered that this small group of eligible patients with the greatest clinical need was defined by a cPRA of 99% or more. MSAC also noted that, for deceased donor kidney recipients, imlifidase would result in displacement i.e. the diversion of a deceased kidney donation from a patient of lower immunological risk to a patient of higher immunological risk, with downstream consequences for the patient not transplanted but who would have been without the introduction of imlifidase.

MSAC noted input that was received from four state and territory governments: [redacted]. These submissions expressed concern with the level and quality of evidence provided for imlifidase, especially the short length of follow-up, small sample size and relevance to the Australian context. They also noted several issues that should be considered, including mechanisms for ongoing data collection, the need for a post-implementation review, the price of treatment, the kidney management algorithm, the need for specialised treatment centres and trained staff, and eligibility and equity considerations.

The submissions also noted that only a small number of patients may be eligible for imlifidase. Specifically:

- [redacted]
- [redacted]
- [redacted]

MSAC also noted the consumer feedback provided by Kidney Health Australia, East Coast Transplant Service and three professional individuals.

MSAC noted that imlifidase is a high-cost drug, with one vial costing approximately [redacted]. Furthermore, most patients require two vials as one dose, and a small percentage of patients require two doses (a cost of approximately [redacted]) because they do not achieve a crossmatch conversion. Implementation is complex with substantially more staff time (potentially out of hours) and reagents to ensure that a crossmatch conversion has occurred. This may also result in:

- more doses being required to reduce donor-specific antibodies to a reasonable level (although, the level is unclear as not all antibodies are equal)
- increased cold ischaemic time for DD kidneys.

MSAC noted that imlifidase does not change the underlying biology of HS patients, and is only used to prevent rejection within the first 6 to 7 days post-transplant. Furthermore, some infusions may not lead to transplantation.

MSAC noted that PASC had previously recommended that the comparator for the patient population on the DD list should be current care defined as remaining on the transplant waitlist and continuing to receive dialysis (haemodialysis or peritoneal), until a transplant becomes

available. MSAC noted that PASC had also previously considered but not recommended inclusion of other desensitisation regimes as comparators for LD patients because components of these regimes are used off label and use is variable across the country (i.e. there is no one standard regime that could be considered as standard of care). However MSAC considered that there were several desensitisation protocols in clinical use for HS patients who are potential recipients of LD and DD kidneys in addition to participation in the paired kidney exchange (for LD kidneys), and many agents were in current clinical use for this indication. MSAC considered that desensitisation protocols (IVIG, rituximab, plasma exchange) were a comparator for Imlifidase, noting the likely cost differential between these agents and imlifidase.

MSAC noted that the clinical evidence for the intervention comprised four single-arm Phase II clinical studies of imlifidase. The data were not disaggregated for LD and DD and the majority of participants in the trials received DD kidneys.

Regarding comparative safety, MSAC noted that the rates of patient withdrawal, loss to follow up and adverse events considered across all trials was 3.7%, 1.9% and 1.9% respectively and the rate for patients who discontinued the study was 9.3%.

Regarding comparative effectiveness, MSAC noted that the data were based on small patient numbers and had limited follow-up. The populations in the clinical trials were relatively heterogenous and MSAC questioned the applicability of the clinical trial data to Australian kidney transplant patients. In particular, the trials included patients with both cPRA 95–99% and cPRA>99%, which meant that the effectiveness of imlifidase in patients with cPRA of 99% or more (the population group who would most likely benefit) was uncertain. MSAC noted that less than 60% of total patients in all trials (27 out of 46) had a cPRA ≥ 99%. Additionally, MSAC considered the effectiveness outcomes to be concerning, especially the rates of hyperacute rejection (33%), delayed graft function (41%), Ab-mediated rejection (24%), and chronic kidney disease at stages 3–5 (50% at 6 months). MSAC noted that this evidence suggested that patients remained at high immunological risk of rejection after treatment.

MSAC noted that the economic evaluation was a model-based cost-utility analysis that was based on unanchored naïve indirect comparisons. MSAC noted several issues with the model:

- the structure of the model did not properly consider the different comparators and correspondingly different clinical pathways for potential recipients of LD and DD kidneys.
- it did not consider displacement in the context of a fixed and limited resource - that is, that the use of imlifidase could displace health gains and impose dialysis costs for non-HS patients on transplant waitlists who would have to wait longer to get a kidney transplant and would correspondingly be deprived of a kidney for longer even though they would have better outcomes following a kidney transplantation.
- it had incomplete costs for a complex implementation as it did not include the cost of extra immunological tests and increased staffing requirements, and delayed or potentially no transplantation outcomes in some cases.
- it was affected by the flow-on effects of using the favourable and unrepresentative data from the clinical evidence base including using extrapolation estimates (for example, for graft survival and survival rates) from pooled clinical trial data that included those who were transplanted in the clinical trials but did not meet the criteria for the “unlikely to be transplanted” population.
- it underestimated the probability of transplantation without imlifidase treatment; the applicant estimated this as 5% per year, but the assessment group noted that data from the ANZ Kidney Exchange indicated a higher rate (e.g. 19.6% by the second year of the projected time horizon).

MSAC agreed with ESC that a main driver of the incremental cost of the model was the total cost of imlifidase. Using a weighted cost of the number of vials (per kilogram) and doses (6.5%

receiving the second dose, assuming that the second dose is costed at double the weighted average price of the first dose) resulted in a cost of $[redacted] per patient per lifetime. Adding the cost of Luminex (PRA assay) testing and comedication increased the cost to $[redacted] per patient per lifetime.

MSAC agreed with ESC that the structure and inputs used for the model made it unreliable for decision-making. MSAC considered that after adjusting the economic model for the displacement effects on non-HS patients identified and the higher costs and inferior outcomes from only extrapolating estimates from the sub-population with the highest clinical need (those with cPRA≥99%) the ICER of DD transplantations facilitated by imlifidase is likely to be in the north-west quadrant (i.e. dominated because it is less effective in health outcomes but also more expensive), while LD transplantations facilitated by imlifidase are likely to be in the north-east quadrant (i.e. more effective in health outcomes but also more expensive).

MSAC noted that the base-case incremental cost-effectiveness ratio (ICER) reported in the applicant-developed assessment report (ADAR) was $[redacted] per quality-adjusted life year (QALY) gained, which MSAC considered implausible given the very high cost of the intervention. MSAC noted that the commentary included a respecified base-case ICER of $[redacted]/QALY gained after accounting for displacement effects on non-HS patients (therefore excluding dialysis cost savings by HS patients) but MSAC still considered this value to be uncertain due to underestimated costs and overestimated benefits arising from the other modelling issues identified above.

MSAC considered the financial impacts of funding imlifidase to be uncertain. MSAC noted that the number of people projected to receive imlifidase in year 1 was 26 from the DD waitlist and 5 from the LD waitlist, increasing in year 6 to 44 and 6, respectively under the ADAR financial estimates. However, MSAC considered that if patients with cPRA 95 to <99% were removed from the estimates in line with a more appropriately restricted population and there were hard caps to restrict use of imlifidase given the high cost of this therapy, this would reduce the proposed number of people receiving imlifidase to a total of around [redacted] a year, comprising [redacted] from the LD list and [redacted] from the DD list consistent with the clinical expert and the submissions from the states. Overall, MSAC considered the likely utilisation to be uncertain.

MSAC also noted that the financial estimates included cost savings due to reduced dialysis that were unlikely to be fully realised because of the displacement issue and not growing the deceased donor pool. MSAC noted that removing these cost savings resulted in a net cost of $[redacted] over 6 years, or almost $[redacted] per year. MSAC also noted that the estimates did not include additional administration or monitoring costs. As noted above, because of the high cost involved, MSAC considered that there should be restrictions on use of this therapy and this should include restricting dosage to one dose (two vials) per patient. MSAC noted that PASC had not recommended a restriction to one dose within the same transplantation attempt as it had considered that there are benefits to having some flexibility in having a second dose available for the small minority of cases where this may be needed at the first and only transplantation attempt. However MSAC considered that the cost and uncertainty was too high not to impose a restriction on doses and/or vials. MSAC considered that advice on clinical place, utilisation caps and costs of the extra immunological testing should be sought from the Renal Transplant Advisory Committee (RTAC).

Overall, MSAC did not support funding for the use of imlifidase in the desensitisation treatment of HS adult kidney transplant patients. MSAC acknowledged that imlifidase may provide some benefit to patients, but there were several major issues and concerns with the submission that made the conclusions about safety, effectiveness and cost-effectiveness of the therapy uncertain. These included:

- The current population restriction was not restricted to those with a clinical need. Patients with cPRA from 95% to less than 99%, who have the highest rate of transplantation given recent changes in allocation algorithms, should not be included in the eligible population. Eligibility should be restricted to patients with cPRA of 99% or more. MSAC noted that while PASC had previously endorsed a cPRA≥95% this had been before the impacts of the recent amendment to the allocation algorithm could be assessed.
- Insufficient attention was placed on potential alternatives as comparators including plasma exchange and other desensitisation protocols differentially applied for potential recipients of LD and DD kidneys.
- The proposed clinical algorithm does not capture the impact of imlifidase on non-HS recipients on the DD waitlist who are displaced.
- Clinical data are uncertain (single arm, short term), have a high risk of bias, and demonstrate an appreciable remaining risk of hyperacute rejection with no change in underlying biology in patients.
- There are implementation issues and costs that need to be considered and included in the model, including more immunological testing, delayed DD transplantation, infusion, and the possibility of no transplantation post infusion.
- The economic model is not useful for decision-making, and both the structure and inputs need to be reworked in light of the suggested amendments to the population, potential differentiation between patients on the LD and DD waiting list after taking account of additional comparators, and to better capture the implementation costs and challenges of administering treatment and the displacement effects on non-HS patients.
- These issues also apply to the financial model as both the economic and financial impacts are likely to overestimate benefits and underestimate costs due to these problems.

MSAC noted that many of the above concerns especially relating to the uncertainty of the clinical evidence and the displacement effects on non-HS patients were shared by the States which provided consultation feedback.

MSAC advised that, before resubmission, the applicant would need to:

- consult with RTAC about the clinical place of the intervention and in particular a revised population, informed by data from ANZDATA which was more reflective of clinical need. MSAC suggested that the applicant consider revising the population restriction to that as framed in the recommendation from the National Institute for Health and Care Excellence (NICE), UK to restrict use to "those who have a positive crossmatch with the donor and are unlikely to have a transplant under the available kidney allocation system (**including prioritisation programmes for highly sensitised people**)." MSAC suggested that such a definition, after accounting for the new algorithm, might limit the eligible population on the DD waiting list to those with cPRA of 99% or more and who have been on the waitlist for more than two years (that is, HS patients who have not received a kidney despite prioritisation) and limit the eligible population who are potential recipients of LD kidneys to those with cPRA of 99% or more who have failed plasma exchange desensitisation treatment so that it is a second line treatment for those who are potential recipients of LD kidneys.
- provide updated clinical data consistent with the proposed new population restriction. This includes follow-up of initial trials, results of new and current Phase III trials (identified by both the applicant and the assessment group), and phase IV data from the United Kingdom and Europe (following the provisional marketing approvals in those countries, further data are to be provided to regulators in 2023 and 2025).
- consider proposing a lower price for the treatment, noting potential other comparators to be explored such as plasma exchange and other desensitisation treatments for patients who are LD and DD kidney recipients and desensitisation enabling participation in paired exchange with Living Related Donors (LRDs).

- revise the economic model. This includes updating assumptions and inputs, revising the extrapolation from clinical data to fit the new proposed population, accounting for displacement effects, using revised comparators, and including costs of additional immunological testing and other implementation challenges.
- restrict payment to a single dose (two vials only) and include a hard cap with 100% rebate limited to [redacted] patients ([redacted] DD and [redacted] LD) per year (but await clinical advice, especially regarding DD transplantations)
- restrict use to centres of excellence in the management of complex immunological risk, such as a single centre in Queensland, two in Victoria, two in New South Wales, one in Western Australia and one in South Australia, consistent with the very high cost of treatment and the high threshold for indications
- consider mechanisms for data monitoring and post-implementation review.

MSAC advised that the resubmission pathway should go through ESC.

4. Background

The Medical Services Advisory Committee (MSAC) has not previously considered imlifidase.

5. Prerequisites to implementation of any funding advice

In the applicant developed assessment report (ADAR), the applicant notes that a Category 1 Type A application has been submitted to the Therapeutic Goods Administration (TGA) to register imlifidase.

On 9 May 2022, imlifidase received orphan designation status and provisional pathway determination. Imlifidase has been submitted for provisional approval for the following proposed indication:

> 'Imlifidase is indicated for desensitisation treatment of highly sensitised adult kidney patients with a positive crossmatch against an available donor prior to kidney transplantation. The use of imlifidase should be reserved for patients who are unlikely to be otherwise transplanted.'

Funding for imlifidase is proposed via the National Health Reform Agreements (NHRA). Subject to a positive recommendation from MSAC, funding agreements will need to be negotiated with each respective state and territory.

On 10 July 2023, the Therapeutic Goods Administration (TGA) approved provisional registration of imlifidase for a period of 2 years. This provisional approval was for the desensitisation treatment of highly sensitised adult kidney transplant candidates prior to kidney transplantation from a donor against whom there is a positive cross-match. The TGA indication also recommended that its use should be reserved for patients who are otherwise unlikely to receive a kidney transplant.

6. Proposal for public funding

Funding is sought for the use of imlifidase in the desensitisation treatment of HS adult kidney transplant patients with a positive crossmatch against an available DD or LD who are unlikely to be transplanted under current kidney allocation systems.

Patients would be eligible for imlifidase if they meet the following criteria:

- active on the deceased and/or living donor list

- calculated panel reactive antibody (cPRA) ≥95%
- positive crossmatch against an available donor
- on the donor transplant wait list for at least one year.

Imlifidase is a cysteine protease derived from the immunoglobulin G (IgG)-degrading enzyme of *Streptococcus pyogenes* that cleaves the heavy chains of all human IgG subclasses but no other immunoglobulins. Cleavage of IgG leads to the elimination of Fc-dependent effector functions, including complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). By cleaving all IgG, imlifidase reduces the level of donor specific antibodies (DSA), thus enabling transplantation.

Imlifidase does not require a Medicare Benefits Scheme (MBS) item number. Funding requested is via the NHRA Addendum for highly specialised therapies. It was agreed by the Joint Chairs' meeting, which includes a State representative, held in June 2022 that imlifidase meets the criteria for funding under the above-mentioned scheme, including:

- TGA-approved medicine to be delivered in public hospitals
- use in the inpatient setting, making it ineligible for listing on the Pharmaceutical Benefits Scheme (PBS)
- high-cost drug, with treatment exceeding A$200,000

In addition, only a subset of kidney transplant units are anticipated to be able to provide imlifidase (with kidney transplantation being a highly specialised service).

7. Population

One PICO set (population, intervention, comparator, outcomes) was defined for imlifidase (Table 1). There are currently no other approved therapies that enable kidney transplantation in HS patients with little or no access to transplantation.

Table 1: PICO criteria for assessing imlifidase for patients unlikely to be transplanted

Component	Description
Population	Adult patients with end-stage kidney disease, who are highly sensitised and unlikely to be transplanted and meet all of the following criteria: • active on the deceased and/or living donor list • cPRA ≥95% • positive crossmatch against an available donor • on the donor transplant list for at least one year.
Prior tests	• histocompatibility tests for active placement on DD waiting list • ongoing patient assessment (on waiting list) • quarterly testing for antibody assessment and crossmatch • crossmatching when a potential DD is identified
Intervention	Imlifidase
Comparator/s	Current care in the absence of imlifidase. These patients (on the active waiting list) will remain on the transplant waitlist and continue to receive dialysis (haemodialysis or peritoneal) until a transplant becomes available, which may or may not occur (transplants will occur but at a decreased rate compared to the intervention).
Outcomes	Safety • Anaphylactic or acute infusion reactions from imlifidase infusion (number of times infusion needs to be ceased for treatment)

Component	Description
	• Serious infection, particularly respiratory infection • Failure to desensitise • Antibody mediated rejection (AMR) and treatment required Effectiveness suggested by the ADAR • Efficacy of crossmatch conversion from positive to negative crossmatch (this should be a pre-transplant outcome) • Graft survival • Kidney function (eGFR) • Adverse effects of treatment • Health-related quality of life Immediate post-transplant • Proportion of patients with cPRA≥95% who received a transplant • Graft viability • Acute antibody mediated rejection (AMR) • Duration of time on waiting list for patients who receive a transplant The following outcomes to be reported in the immediate-, medium- and longer-term • Graft survival • Patient survival • Proportion of patients on dialysis and/or reduced time on dialysis • Hospitalisation • AMR (outcome reported to OrganMatch site) Cost-effectiveness Healthcare resources The main costs are related to: • Cost of imlifidase • Cost of kidney transplant • Ongoing costs of dialysis • Inpatient hospitalisation
Assessment questions	What is the safety, effectiveness and cost-effectiveness of imlifidase compared to no imlifidase in highly sensitised patients unlikely to be transplanted?

Abbreviations:
AMR = Antibody mediated rejection; **cPRA** = calculated panel-reactive antibody; **DD** = deceased donor; **eGFR** = estimated glomerular filtration rate.

The intended population for imlifidase consists of patients actively registered on DD and/or LD lists, irrespective of donor characteristics (donor-agnostic), with a cPRA ≥95% and a positive crossmatch. Patients must have spent a minimum of one year on the DD waitlist and/or the Australian and New Zealand Kidney Exchange (ANZKX) for LDs. These criteria define a pool of potential candidates from which a treating physician specifically identifies imlifidase recipients, after confirming that all other transplant options have been thoroughly explored.

In light of the most recent waitlist statistics MSAC has recommended that patients with cPRA 95–99%, who have the highest rate of transplantation given recent changes in allocation algorithms, should not be included in the eligible population and eligibility should be restricted to patients with cPRA of 99% and above. MSAC further considered that for those on the LD waiting list, eligibility should also be limited to who have failed plasma exchange desensitisation treatment. MSAC recommended that the final specifications should be dependent on the results of consultation with RTAC.

8. Comparator

No equivalent therapy enables kidney transplantation in HS patients with little or no access to transplantation. The commentary agreed that the comparator to imlifidase is continuation on the transplant waitlist for patients who will receive ongoing dialysis treatments (either haemodialysis or peritoneal) until a transplant becomes available. These patients remain active on the waiting list. Although transplants will still occur, they will occur at a reduced rate compared to those receiving imlifidase.

The commentary noted that effectiveness and safety data for the comparator could not be obtained from a single source, as it pertains to a specific subpopulation of HS patients on transplant waiting lists for at least one year. These patients either continue with haemodialysis or, in a limited number of cases, undergo transplantation after spending over a year on the waiting list.

However MSAC considered that insufficient attention was placed on potential alternatives as comparators including plasma exchange and other desensitisation protocols for patients who are LD and DD kidney recipients and desensitisation enabling participation in paired exchange with Living Related Donors (LRDs).

9. Summary of public consultation input

Consultation input was received from 1 professional organisation, 1 consumer organisation and 3 individuals (1 consumer and 2 medical professionals). The following organisations submitted input:

- Kidney Health Australia
- Prince of Wales Transplant Unit, East Coast Transplant Service

The consultation feedback received was all supportive of public funding for imlifidase as a desensitisation treatment to enable kidney transplant in HS adult transplant candidates.

Clinical need and public health significance

- The main benefits of public funding noted in the consultation feedback were related to the benefits of kidney transplantation and no ongoing need for dialysis. This included:
  - improved quality and quantity of life after kidney transplantation for the recipient and their family
  - improved equity, as it provides an additional option for desensitisation for HS patients
  - avoiding dialysis (a restrictive treatment), allowing patients to return to work and other roles
  - imlifidase intervention unavailable if not publicly funded
  - successful transplantation using imlifidase is cost-saving in the long-term, as dialysis is a costly service
- The main disadvantages of public funding as received in the consultation feedback included:
  - lack of long-term data
  - intense post-transplant monitoring (e.g. biopsies, monitoring for rejection in the first year)
  - potential for unsuccessful treatment compromising graft survival
  - general risks associated with transplantation
  - resource allocation (i.e. allocation of a transplant that could have otherwise gone to an alternate recipient where the risk of antibody rejection and associated graft failure, at least at the outset, is much lower)

- Other services identified in the consultation feedback as requiring delivery before or after the intervention included:
  - pathology testing services before and after transplantation including tissue typing, crossmatching and anatomical pathology for biopsy review
  - surgery
  - assessment by dietitian, psychologist and exercise physiologist; education via transplant nursing coordinators
  - drug therapies post-transplantation
  - plasma exchange services
  - ongoing postoperative monitoring for antibody mediated rejection.

Additional comments

One specialist stated that from the perspective of equity of access, it is important to allow access to new therapies such as the proposed intervention, particularly for patients who have limited other options.

The Prince of Wales Transplant Unit, East Coast Transplant Service, stated that it may be more equitable if the treatment is available to all units, as opposed to specialised transplant centres.

One specialist stated that with appropriate collaboration with tissue typing services, HS patient profiles can be reviewed and transplant teams can identify which specific antibodies can be managed, adding that plasma exchange, IgG and B cell-depleting therapies can be employed to treat any post-transplant rise in antibodies.

Consumer Feedback

One consumer described the impact kidney disease and dialysis treatment has had on all aspects of their life. They stated that having access to this treatment would improve their own quality of life and relationships with family. They added that access to the proposed intervention would remove some of the hurdles they have faced and allow them to feel more fulfilled in work and general living. They noted that receiving a kidney, with maintenance in the form of medication, would be worthwhile despite any possible disadvantages.

10. Characteristics of the evidence base

The clinical evidence presented in the submission was primarily based on 4 phase-II clinical studies of imlifidase (13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04, and 15-HMedIdeS-06) listed in Table 2.

Table 2: Key features of the included evidence

Trial/Study identifier	N	Study design Risk of bias	Population	Intervention	Comparator	Key outcome(s)	Result used in economic model
Intervention Arm							
Combined imlifidase trial data from: • 13-HMedIdeS-02 • 13-HMedIdeS-03 • 14-HMedIdeS-04 • 15-HMedIdeS-06 Additional retrospective data collection on 13-HMedIdeS-02 and 13-MedIdeS-03 in: • 17-HMedIdeS-13: Long-term follow-up study of imlifidase trials • 17-HMedIdeS-14	30	Single arm, prospective phase-II trials. Data combined to include all patients in the population. Moderate risk of bias (single arm studies)	UTT-A HS patients with cPRA ≥95%, positive crossmatch, DD or LD transplant	HLAi transplant with Imlifidase	-	Crossmatch conversion. % Patients receiving a transplant. Patient survival Graft survival Graft rejection over time due to AMR. Kidney function (GFR) TEAEs, related TEAEs	All-transplanted patients (N=46): graft survival, patient survival, AMR, delayed graft function AEs (N=54: all-imlifidase population) Scenario analyses using UTT-A and UTT populations.
	25		UTT HS patients with cPRA ≥95%, positive crossmatch, DD transplant:				
	46		All-imlifidase HS transplanted patients				
Comparator Arm							
Current Care For the small percent of patients receiving a delayed transplant, imlifidase transplant-enabled outcomes are utilised.	46	TSANZ: database. Low risk of bias (single arms). Single arm, prospective phase-II trials. Data combined to include all patients in the population. Low-moderate risk of bias (single arms)	Australian HS patients on DD waiting list and patients on dialysis (± delayed transplant)	46	Remain on dialysis. OR Remain on dialysis with a delayed transplant.	Patient survival Graft survival AEs	TSANZ data 44th report (dialysis mortality 2020-21 tables) Patient survival by age. Combined imlifidase study data.

Abbreviations:
AMR = antibody mediated rejection; **DD** = deceased donor; **GFR** = glomerular filtration rate; **HLAi** = human leucocyte antigen incompatible; **HS** = highly sensitised; **LD** = live donor; **TEAE** = treatment-emergent adverse event; **UTT-A** = unlikely to be transplanted–agnostic (in the absence of imlifidase) including both deceased and live donor transplants; **UTT** = unlikely to be transplanted (in the absence of imlifidase), including only deceased donor transplants

The commentary considered that these studies may be subject to bias. Given the small study population, the findings may not always be generalisable to other populations, such as the Australian population.

The commentary acknowledged the absence of long-term data and highlighted that the applicant is conducting two phase-III trials. These ongoing phase-III trials, led by the sponsor, have the potential to address existing knowledge gaps and may ultimately help determine the benefit-risk balance of the treatment. By providing more comprehensive information, these trials could offer a more robust understanding of the treatment's long-term efficacy and safety in various populations, including those outside the initial study settings. However, results of phase-III clinical trials are currently unavailable, and as such uncertainty associated with the existing phase-II clinical trials is impactful in the evaluation of imlifidase.

11. Comparative safety

The clinical evidence presented in the ADAR was primarily based on 4 phase-II clinical studies of imlifidase reported (13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04, 15-HMedIdeS-06).

The ADAR included a safety dataset consisting of a broader group of patients in the safety analyses. The safety dataset comprises a more extensive patient group: the chronic kidney disease (CKD) all-imlifidase population. This group encompasses all patients in the study program who received at least one dose of imlifidase (N=54), constituting the complete safety set in the combined analyses. A summary of patients in the all-imlifidase safety dataset is provided in Table 3.

Table 3: Summary of patients in safety dataset

	13-HMedIdeS-02	13-HMedIdeS-03	14 HMedIdeS-04	15-HMedIdeS-06	All-Imlifidase Total safety set (N=54)	All-Transplanted (N=46)	UTT-A (N=30)	UTT (N=25)
Received at least one dose of imlifidase, n (%)	8	10	17	19	54	46	30	25
Received transplantation, n (%)	1 (12.5%)	10 (100.0%)	17 (100.0%)	18 (94.7%)	46 (85.2%)	46 (100.0%)	30 (10.0%)	25 (100.0%)
Did not receive transplantation, n (%)	7[a] (87.5%)	0	0	1[b] (5.3%)	8 (14.8%)	0	0	0
Completed core study, n (%)	8 (100.0%)	10 (100.0%)	15 (88.2%)	16 (84.2%)	49 (90.7%)	42 (91.0%)	23 (92.0%)	28 (93.0%)
Drug withdrawal/dose interruption, n (%)	1 (12.5%)	0	0	3 (15.8%)	4 (7.4%)	2 (4.0%)	2 (8.0%)	2 (7.0%)
Discontinued study, n (%) AE Lost to follow-up Other[c] Patient withdrew	0	0	2 (11.8%) 0 1 (5.9%) 0 1 (5.9%)	3 (15.8%) 1 (5.3%) 0 1 (5.3%) 1 (5.3%)	5 (9.3%) 1 (1.9%) 1 (1.9%) 1 (1.9%) 2 (3.7%)	4 (9.0%) 0 1 (2.0%) 1 (2.0%) 2 (4.0%)	2 (8.0%) 0 0 0 2 (8.0%)	2 (7.0%) 0 0 0 2 (7.0%)

Abbreviations:
AE = adverse event; **UTT** = unlikely to be transplanted; **UTT-A** = unlikely to be transplanted–agnostic
Notes:
a) Transplantation was NOT a prespecified part of the trial protocol and only occurred at the investigators' discretion if the possibility became available.
b) One patient did not receive a transplant following an infusion-related reaction (serious adverse event) with imlifidase that resulted in treatment and study discontinuation.
c) One subject experienced graft failure and decided not to complete the study. One patient treated (0.25 mg/kg) but not transplanted in Study 13-HMedIdeS-02, was included in 13-HMedIdeS-03 1.5 years later and was treated (0.50 mg/kg) and transplanted.

Imlifidase is administered in a clinical environment where numerous factors, including underlying disease, immunosuppressive treatments, hospitalisation and transplantation, can contribute to a broad range of adverse events (AEs) and safety concerns. The AEs observed in imlifidase trials were manageable and no life-threatening severe AEs occurred during the clinical program. Two patients (7%) in the UTT-A (unlikely to be transplanted–agnostic to donor type, i.e., those who meet the PICO criteria which includes those on both the living donor and deceased donor transplant waiting lists) subpopulation reported related treatment-emergent severe AEs, both receiving kidney grafts from living donors, while none were reported in the UTT (unlikely to be transplanted – deceased donor waiting list only) population. In the all-imlifidase population safety dataset (N=54), the category with the highest frequency of treatment related treatment-emergent AEs was 'infections and infestations' (17%). Related treatment-emergent AEs reported by more than one patient included urinary tract infections (6%) and sepsis (4%).

Similar to other intravenously administered antibody-based agents, infusion-related reactions may occur during imlifidase infusion. To minimise this risk, glucocorticoids and antihistamines are given before dosing. AEs of particular interest included severe or serious infections (15.2%) and infusion-related reactions (2.2%), as reported for the all-transplanted population. The outlined toxicities are deemed manageable.[1]

Transplantation-related events, such as delayed graft function and graft rejection, are anticipated following kidney transplantation, particularly in recipients of DD organs and those undergoing their second or subsequent transplant. The risks of these events may be increased in patients receiving imlifidase due to increased cold ischaemia as a result of delays in transplantation due to imlifidase administration and additional testing required, in comparison with current practice.

The ADAR also includes data from the 17-HMedIdeS-14 study, an observational follow-up investigation designed to collect long-term data (up to 5 years) from all transplanted patients involved in the imlifidase studies. Medical centres that participated in imlifidase research and conducted patient transplants post-imlifidase treatment (known as 'feeder studies') were contacted and requested to engage subjects for enrolment in this study. Of the 46 patients transplanted in the feeder studies, 29 have been actively enrolled in the 17-HMedIdeS-14 study (as of data cut-off date 30 September 2019). Data from an additional 6 patients (3 experiencing graft loss and 3 who died after the feeder studies but before initiation of 17-HMedIdeS-14) are presented (Table 4), as approved by the Institutional Ethics Committees/Institutional Review Boards of the respective trials.

[1] European Medicines Agency. 2020. Imlifidase - Summary of product characteristics (SmPC) and European public assessment report (EPAR) [Online]. https://www.ema.europa.eu/en/documents/product-information/idefirix-epar-product-information_en.pdf. Available: https://www.ema.europa.eu/en/documents/product-information/idefirix-epar-product-information_en.pdf [Accessed May 2022]

Table 4: Summary of patients in safety dataset in patients followed up, study 17-HMedIdeS-14

	13-HMedIdeS-02 (N=1)	13-HMedIdeS-03 (N=10)	14-HMedIdeS-04 (N=11)	15-HMedIdeS-06 (N=13)	Total (N=35)[a]
	n (%)	n (%)	n (%)	n (%)	n (%)
Full analysis set	1 (100%)	10 (100%)	11 (100%)	13 (100%)	35 (100%)
Completed	1 (100%)	0	0	0	1 (3%)
Ongoing	0	9 (90%)	7 (64%)	12 (92%)	28 (80%)
Discontinued	0	1 (10%)	4 (36%)	1 (8%)	6 (17%)
Graft loss		0	3 (27%)	0	3 (9%)
Death		1 (10%)	1 (9%)	1 (8%)	3 (9%)

Notes:
N=all subjects; n=subjects with data; %=n/N.
[a] represents 35 of the 46 patients in the all-transplanted group that were followed up at year 2.

The commentary considered that using imlifidase leads to safety outcomes that are at least non-inferior but that the lack of longer-term data raises concerns about the potential long-term safety issues associated with imlifidase therapy. The commentary considered that while the existing evidence provides a foundation for understanding the treatment's safety, further research with larger sample sizes and extended follow-up periods would be valuable to substantiate the findings and to better evaluate the long-term safety profile of imlifidase in the context of kidney transplantation.

12. Comparative effectiveness

Limitations of the submitted evidence

Imlifidase studies included in the ADAR

Despite their non-randomised and non-controlled design, the commentary agreed that the imlifidase trials were structured suitably to minimise quality-related concerns. The commentary acknowledged that the primary clinical evidence for imlifidase comes from 4 uncontrolled, open-label studies, which have inherent, well-known potential limitations in their quality. The commentary agreed that randomised controlled trials were deemed infeasible due to the nature of imlifidase treatment and the ethical considerations surrounding the lack of a suitable, safe and effective comparator. Limited availability of donor organs and variations in kidney allocation systems across countries are additional obstacles to conducting a randomised controlled trial. Given these constraints, the trials were performed in a methodologically sound manner, considering the challenges posed by imlifidase therapy.

The commentary noted that the small sample size in the studies is a limitation, which may affect the generalisability of the results. Additionally, the lack of longer-term data raises concerns about the durability of the treatment effects and the potential long-term safety issues associated with imlifidase therapy. While the existing evidence provides a foundation for understanding the treatment's efficacy and safety, further research with larger sample sizes and extended follow-up periods would be valuable to substantiate the findings and to better evaluate the long-term benefits and risks of imlifidase in the context of kidney transplantation.

Utility values

The commentary considered that utility values identified in the studies are not specific to HS patients, which introduces uncertainty in assessing treatment benefits for this particular population. To better understand the effectiveness and cost implications of imlifidase therapy for HS patients, more targeted studies that account for these patients' unique challenges and circumstances are needed. This would help to address the existing uncertainties and provide a more accurate representation of the impact on patient outcomes and healthcare costs.

Systematic reviews

The commentary considered that multiple methodological concerns are associated with the systematic review presented in this ADAR. While the systematic review is thorough in its presentation and methodology, inconsistencies in reporting the results are observed across tables, search results, and the PRISMA. Consequently, it remains uncertain whether all pertinent evidence has been considered. Overall confidence in the systematic review results is deemed to be moderate, with more than one non-critical weakness.

In its pre-ESC response the applicant clarified aspects of its systematic review and the assessment group accepted that the clarification satisfactorily addresses the concerns raised.

Expert opinions

The commentary considered that the methods employed for gathering expert opinions do not fully adhere to the stipulations outlined in Table 36 of the MSAC Guidelines. Specifically, there is a lack of information regarding the criteria for selecting advisors, the number of experts approached, the dates when expert opinions were obtained, declarations of potential conflicts of interest from each participant whose opinion was sought, and any background information provided to the experts and its consistency with the evidence presented in the submission. Additionally, it is not stated whether advisors received compensation for their time. The commentary also noted discrepancies in the information given to each expert and the format used to solicit their input. Furthermore, experts were not asked about the applicability of the study population to the Australian context or practical considerations related to incorporating imlifidase into their respective centres.

However the applicant's pre-ESC response disputed some of these claims, noting that:

- the declarations of interest of the two clinical experts interviewed were provided and mentioned that they were compensated for their time;
- the ADAR provided information on the reason those two experts were selected and noted that the difference in the number of questions asked of the experts was because one was not available for the follow-up meeting;
- the ADAR described the decision process in case of inconsistency across experts.

Clinical claim

The clinical claim made by the ADAR is:

- use of imlifidase results in superior effectiveness compared with current care (absence of imlifidase, which includes remaining on the transplant list, ongoing dialysis and possibility of delayed transplantation, which may or may not occur, and if it does occur will be at a decreased rate compared with the intervention)
- use of imlifidase results in at least non-inferior safety.

The commentary concluded that the efficacy evidence presented sufficiently supports the claim that imlifidase results in superior effectiveness compared with current care in the absence of imlifidase.

The ADAR (and commentary) recognises that assessing the adverse effect profile is difficult, given that patients in both arms experience AEs of different types and frequencies. Moreover, the commentary recognised that obtaining long-term data on graft survival can be challenging, as it requires ongoing monitoring of patients over many years and may be subject to various confounding factors.

The ADAR states that data reported in the naïve indirect comparison is used in the comparative modelled evaluation to support a claim of superior effectiveness over current care. The ADAR further reports that the ITC is assessed as moderate quality (GRADE criteria) compared to the Australian highly sensitised program (HSP) waiting list. The imlifidase combined populations had generally similar baseline characteristics.

The commentary accepted the rationale for a naïve indirect treatment comparison; however, the commentary disagreed with the conclusion drawn by the ADAR that the patient characteristics are generally homogeneous between the imlifidase study population and the Australian comparator population. There are material differences between the median age (43.3 vs 49 years old), duration of dialysis (6.1 vs 3.7 years), comorbidities (96% with cardiovascular disease vs 17.7% with coronary artery disease, 8.1% with peripheral vascular disease, and 6.1% with cerebrovascular disease) and retransplant rates (30% vs 77% with no previous transplant) that add considerable uncertainty to the assessment of relative treatment effectiveness. The commentary further highlighted several unobservable differences in prognostic factors that should be considered when assessing bias in an unanchored indirect treatment comparison.

The commentary considered the evidence for comparative clinical effectiveness to be at high risk of bias due to residual confounding, equivalent to evidence from observational studies typically assessed as low quality (GRADE criteria).

In its pre-ESC response, the applicant reiterated that imlifidase demonstrated efficacy in all patients for which the appropriate dose was provided per the licensed indication, regardless of patient characteristics including ethnicity, level of cPRA, and age. The pre-ESC response also argued that comorbidities, duration of dialysis, and retransplant rate parameters specifically highlighted by the commentary have no impact on the crossmatch conversion with imlifidase and that the differences in these parameters bias the result toward a more conservative estimate of imlifidase transplant outcomes. However the assessment group maintained that although the treatment effect of imlifidase may be consistent across these population groups, differences in prognostic characteristics (both observed and unobserved) have the potential to confound the comparison, even if they are not treatment effect modifiers, as the underlying risk in each population is different and that therefore significant uncertainties with the ITC remained.

Clinically important outcomes

The ADAR presents imlifidase clinical trial data for multiple populations including the UTT population (PICO DD only; N=25), the UTT–agnostic to donor population (N=30), the all-transplanted population (N=46) and the all-imlifidase safety dataset (N=54) to provide comprehensive outcomes assessment.

The ADAR identifies data on the achievement of transplantability in sensitised patients; graft survival, graft function and patient survival after transplantation are deemed the most clinically

significant outcome parameters. These outcomes have been recognised in the approved PICO and are featured as key clinically relevant outcomes in this section, along with other outcomes of interest identified by the PICO. Each key outcome is discussed below.

1: Crossmatch conversion and DSA elimination

Crossmatch conversion was an important outcome in the clinical trials of imlifidase. In the UTT and UTT-A patient subpopulations, all dosed patients were rapidly and successfully converted to a negative crossmatch, allowing transplantation to occur in all patients.

Data on DSA levels from study 15-HMedIdeS-06 shows that despite similar DSA levels before transplantation, US patients experienced a significant reduction in post-transplantation DSA compared to the Swedish population. This was explained as being likely due to the use of intravenous immunoglobulin and rituximab in US patients before and after transplantation.[2] The commentary noted that this difference in standard of care post-transplantation (use of intravenous immunoglobulin and rituximab) might lead to a bias in the assumed efficacy of imlifidase. In both studies (13-HMedIdeS-02 and 13-HMedIdeS-03) all patients displayed a rapid reduction of both B- and T-cell panel reactive antibody (PRA) levels; however, there was large individual variation in the rate of PRA recovery.

2: Proportion of patients with cPRA ⩾95% who received a transplant

The ADAR uses a patient's anti-HLA antibody profile and data from the Eurotransplant database to estimate the likelihood of any patient being offered a compatible donor. The ADAR estimates that 13 patients (52%) had 0% compatible donors in the Eurotransplant database, 17 (68%) had <0.075% and 24 (96%) had <1%. The commentary noted that the degree to which the Eurotransplant database reflects the Australian patient population is unclear. In Section 4, the ADAR also states that 43.6% of those patients with cPRA 95–98% who are on the Australian DD waitlist are transplanted in the first year (Sypek MP et al. 2021).[3] Large discrepancies exist between estimations made by the ADAR and the percentage of HS patients on the Australian DD waitlist who receive a transplant in the first year. The commentary found it is currently unclear exactly which variables are causing the study population to have such a low estimation of compatible donors compared to the data of Sypek MP et al. 2021.

3: Patient survival

All patients in the UTT and UTT-A populations were alive at the end of the clinical trial period (6 months); however, 3 patients died after this time. The ADAR did not present any reason to assume that any death was related to the administration of imlifidase or due to kidney malfunction.

The 3-year long-term imlifidase study follow-up data showed an overall patient survival rate of 84% (UTT) to 87% (UTT-A). In the larger all-transplanted imlifidase population, survival was 92% at year 3, being similar to survival seen in the Canadian HS program.

[2] Jordan SC, et al. (2017). 'IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation.' *New England Journal of Medicine*, 377(5):442-453.

[3] Sypek MP, et al. (2021). 'The Introduction of cPRA and Its Impact on Access to Deceased Donor Kidney Transplantation for Highly Sensitized Patients in Australia.' *Transplantation*, 105: 1317-1325

Long-term patient survival following transplantation in Australia is higher than in the US[4] and comparable to Sweden.

The commentary noted that the ADAR's speculation of higher survival outcomes if the trial was conducted in Australia is unfounded and is not supported by a reference.

The overall similar graft survival rates seen in Australia and Canada for all transplants suggests that Canadian HSP survival data may be reasonably consistent with expected Australian HSP transplant survival data. In addition, the commentary noted that the imlifidase trial UTT-A population 3-year survival rate of 87% appears comparable to the Canadian HSP population survival rate, making the Canadian HSP data a reasonable proxy.

Based on the similarity of the survival outcomes in Sweden and Canada to the imlifidase study follow-up data (3-year survival of 87% in the UTT-A population and 92% in the all-transplanted population), the ADAR concluded and the commentary agreed that it is reasonable to conclude that the imlifidase data can be generalised to Australian imlifidase use in the proposed setting. The commentary noted that the ADAR claimed that this was supported by expert opinion input, but did not supply any evidence for the claim.

4: Graft survival

In the imlifidase studies, a total of 6 patients in the all-transplanted population experienced graft failure. Three of these graft failures occurred in the initial 6-month trial period, of which one occurred in a patient in the UTT and UTT-A subpopulations. The further 3 graft failures occurred during the 2–3-year follow-up period. Two of these failures occurred in patients in the UTT and UTT-A populations. No graft failures occurred in the time period between 6 months and 2 years follow-up.

The ADAR provides comparisons of graft survival of imlifidase populations with data from other countries. Graft survival in the imlifidase UTT-A population (97% at 6 months, 97% at 1 year, 91% at 3 years) shows good comparability with Australian overall graft survival (96% at 6 months, 94% at 1 year, 82% at 5 years) and also compares favourably with survival at 3 years in the Canadian HSP program. It is reported in the ADAR that Australian graft survival rates are high compared to international standards.

The commentary noted that graft survival rates reported in the ADAR from the HS patients found in the imlifidase studies seem to be reasonably consistent with those found in the Australian overall kidney transplantation data provided in Table 23 of the ADAR. Given that there is a high retransplant rate in the imlifidase study population, and that retransplantation is associated with reduced graft survival, it was agreed by the commentary that the rates of graft survival found in the imlifidase study population provide evidence to support the use of imlifidase to enable HLA-incompatible transplants to occur in Australian 'unlikely to be transplanted' HS patients.

5: Graft rejection over time due to antibody-mediated rejection

Because imlifidase acts to lower DSA levels during the initial period of transplantation and is not expected to impact other rejection events, antibody-mediated rejection (AMR) was not considered in the ADAR to be a study primary efficacy outcome and was considered a safety consideration. The commentary agreed with this categorisation. In total, 10 patients in the UTT-A and UTT populations experienced AMR during the 6-month study period, with 2 reported as subclinical. All instances of AMR were successfully treated using standard therapies according to local practice.

[4] Merion RM, et al. (2018). 'Kidney transplant graft outcomes in 379 257 recipients on 3 continents.' *American Journal of Transplantation*, 18: 1914-1923.

No grafts were lost due to active AMR at 6 months. The commentary noted that the standard of care used to treat AMR may not be generalisable to an Australian population.

It was agreed by the commentary that graft failure due to AMR can be considered a clinically important AE in Australia, given the data provided by the ADAR that acute rejection as the cause of graft failure was reported in 14% of graft losses in the first year and 4% beyond the first year.

The ADAR noted that AMR rejection rates in Australia vary according to the type of transplant and vary across reported years in the ANZDATA registry. The ADAR also provides data, supported by the European Medicines Agency (EMA), that in HS patients the reported frequency of AMR varies from 12% to 61%. The commentary noted it is difficult to compare the rate of AMR seen in the imlifidase study to Australian patients eligible to receive the treatment. The commentary acknowledged and accepted that rates of AMR from the UTT-A subgroup (30%) are broadly consistent with the variable frequency of HS patients reported (12–61%), however, it is still unclear how generalisable this data is to an Australian population.

Finally, the ADAR states that treatment for AMR that was inputted into the economic model was validated with 2 experts providing advice. After review, the commentary considered that the methods used to collect expert opinion as reported is not fully in line with the guidelines for preparing MSAC assessments.

6: Kidney function by glomerular filtration rate

Estimated glomerular filtration rate (eGFR) calculated from serum creatinine levels was used as an outcome measure for kidney function and evaluated for all patients who underwent transplantation. The ADAR reports that generally kidney function was 'satisfactory' at 6 months after transplantation for the great majority of patients. No supporting information was provided to describe what constitutes satisfactory kidney function.

The commentary noted that the definition of satisfactory kidney function is not explicitly mentioned and it is unclear from where this term is derived. It is recommended to clarify the criteria for satisfactory kidney function and assess its relevance in the context of these study populations.

7: Delayed graft function

Among the 43 patients from the all-transplant group with a functioning graft at 6 months, 19 (44%) had experienced delayed graft function (DGF) after transplantation, with persistence varying from 1 day to several weeks and months. There was no apparent relationship between the occurrence or length of DGF and cold ischemia time or kidney donor profile index.

In the literature, the incidence of DGF can greatly vary among centres from 3.2% to 63.3%.[5] One US study found that the duration of DGF, rather than DGF itself, was associated with graft survival.[6]

The commentary noted that no clinical justification was provided for the clinical experts' view that the duration of DGF is shorter on average in Australia than in the US where many of the trial patients were transplanted. The commentary stated that it is unclear whether such a general

[5] Orandi BJ, et al. (2015). 'Center-level variation in the development of delayed graft function after deceased donor kidney transplantation.' *Transplantation*, 99: 997-1002.

[6] Budhiraja, P. et al. (2022). 'Duration of delayed graft function and its impact on graft outcomes in deceased donor kidney transplantation.' *BMC Nephrology,* 23: 154.

country comparison is appropriate, given that the incidence rate of DGF varies greatly between centres (3.2–63.3%).

8: Quality of Life

Health-related quality of life (HRQoL) has been identified as a crucial transplant outcome priority by Australian healthcare professionals and community members[7] and was recognised as a key benefit of transplantation for patients and carers during the PICO consultation. The commentary noted that the imlifidase phase-II studies did not collect HRQoL data. The commentary observed that although HRQoL data was collected in the follow-up study 17-HMedIdeS-14, health state utility decrement values used in the model were derived from a targeted literature review, rather than utilising the HRQoL data from the trial. The reason for this approach is not clearly explained, except for a suggestion that the available data may have been sparse, with some patients having had only one visit. Further clarification would be helpful to understand the rationale behind this decision and its potential impact on evaluation outcomes.

13. Economic evaluation

Cost-utility analysis

The ADAR presents a cost-utility analysis to quantify the additional costs and benefits of treatment with imlifidase prior to kidney transplant in HS individuals (cPRA ≥ 95%). A cost-utility analysis is appropriate for the decision, given the evidence of superior effectiveness compared with current care in the absence of imlifidase. The economic evaluation utilises a cohort-level Markov state transition model developed in Microsoft Excel to estimate the costs and clinical benefits of increased kidney transplantation rates in the target population. The model includes health states describing patients receiving dialysis, those on and off the kidney transplant waitlist, patients with a functioning graft and death (Figure 1). In addition to the direct health benefits to patients who receive imlifidase, the model also considers spill-over benefits in the form of completed living donor chains administered through ANZKX, with a proportion of patients receiving imlifidase assumed to be included in living donor chains completed following successful treatment with imlifidase. The benefits to other patients in these completed donor chains are also included in the ADAR when evaluating the benefit of treatment with imlifidase.

[7] Sypek MP, et al. (2022). 'Healthcare professional and community preferences in deceased donor kidney allocation: A best-worst scaling survey.' *American Journal of Transplantation*, 22: 886-897.

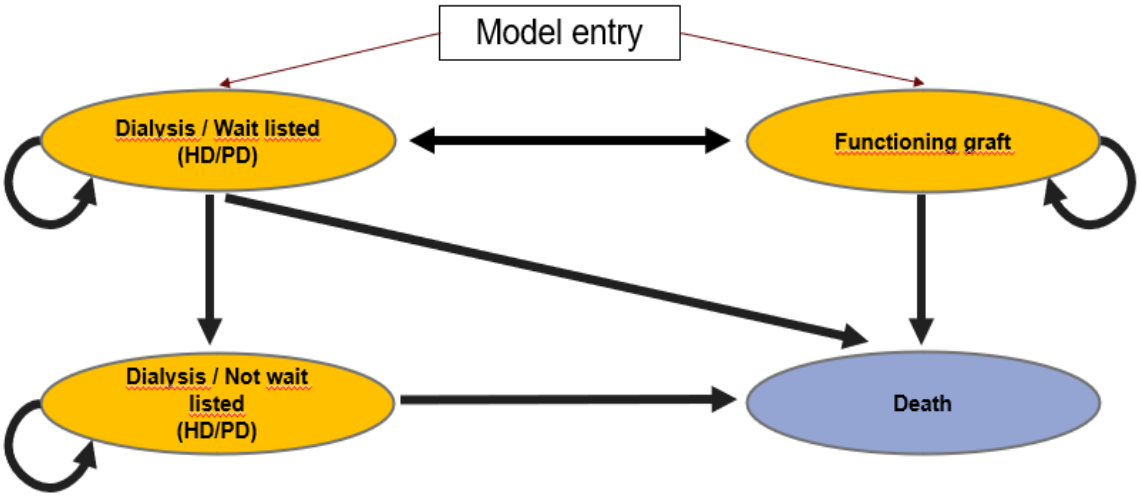

Figure 1: Cost-utility model schematic

Transitions between model health states were informed by analysis of individual patient data from the imlifidase trial program and registry data from ANZDATA and ANZKX. Health states were assigned costs and utility values sourced from published literature, with time spent by patients in each health state informing overall costs and benefits accrued over a lifetime model horizon (6-month model cycle length). Table 5 shows a summary of the cost-utility model submitted.

Table 5: Summary of the economic model included in the evaluation

Component	Description
Perspective	Australian healthcare system
Population	Patients with ESKD who are highly sensitised and unlikely to be transplanted and: • active on the DD and/or LD list • have cPRA ≥95% • a positive crossmatch against an available donor • been on the DD transplant waitlist and/or the ANZKX program for at least one year.
Prior testing	Luminex single antigen bead testing or flow cytometry crossmatch
Comparator	Submission refers to current care in the absence of imlifidase.
Type(s) of analysis	Cost-utility analysis
Outcomes	Life years gained, quality-adjusted life years gained, successful conversion, time to graft failure, time on dialysis avoided and treatment emergent adverse events
Time horizon	Lifetime (58 years in the model base case)
Computational method	Cohort level Markov state transition model
Generation of the base case	Trial-based evaluation used to provide the base case
Health states	• Dialysis/waitlisted: patients on the DD transplant waitlist or ANZKX program and on dialysis • Dialysis/not waitlisted: patients still on dialysis but no longer on the DD transplant waitlist or ANZKX program • Functioning graft: patients with a functioning kidney graft • Death
Cycle length	6 months

Component	Description
Transition probabilities	Graft and patient survival for patients with a functioning graft estimated based on extrapolations from the ongoing imlifidase prospective, observational long-term study. Probability of transplant following administration of imlifidase is based on pooled clinical trial data. Probability of transplant without imlifidase is assumed based on Australian clinical expert opinion, as well as Cantwell et al. (2015)[1] and the ANZDATA Regiaret 44th annual report (2021). Probability of death in patients receiving dialysis is based on ANZDATA 44th annual report (2021).
Discount rate	5% for both costs and outcomes
Software	Excel

1. Cantwell L, et al. (2015). 'Four years of experience with the Australian kidney paired donation programme.' *Nephrology* 20(3): 124-131

Abbreviations:
ANZKX = Australian and New Zealand Kidney Exchange, **cPRA** = calculated panel-reactive antibody, **DD** = deceased donor, **ESKD** = end-stage kidney disease, LD = living donor

Source:
ADAR Table 37 and compiled for the commentary

The described model structure is generally appropriate to address the decision problem as configured by the ADAR; however, the commentary disagreed that the analysis presented in the submission aligned with the perspective of the Australian healthcare system, as stipulated in MSAC guidelines. In particular, while the model estimates cost offsets associated with the target population ceasing dialysis upon receipt of a donor kidney due to imlifidase, it ignores the effects this has on other potential recipients of the donor kidney on the transplant waiting list outside the target population who will have to continue dialysis due to the scarcity of donated kidneys. The cost offsets included in the ADAR as a result of reduced dialysis provision are illusory and unlikely to be fully realised by the healthcare system in Australia.

Although opportunity costs incurred outside the target patient population are routine when deciding allocation of healthcare resources and are not typically considered in cost-utility analyses, these costs are generally distributed across the entire general population, and it is usually assumed that adjustments can be made to accommodate overall changes in demand. However, in this case, the scarcity of donor kidneys means that there is a direct and tangible impact on other non-HS patients waiting to receive a donor kidney. Whilst the ADAR acknowledges these potential negative spill-over effects on the non-target population, there was no attempt in the ADAR to explore these wider implications of scarcity of donated kidneys in quantifying the benefits and costs associated with administering imlifidase in an HS patient cohort.

Similarly, although the clinical trial program supports significant health benefits for HS patients treated with imlifidase, the analysis neglects to consider the incremental outcomes associated with providing a donor kidney to another patient on the transplant waiting list, particularly as HS patients are likely to experience poorer health outcomes following transplantation. Inclusion by the ADAR of spill-over benefits associated with completed chains contrasts with the exclusion of spill-over costs and negative outcomes associated with not providing a donor kidney to a non-HS patient.

While it is plausible there may be an overall reduction in waitlist times following the introduction of imlifidase even after taking account of the impacts on the non-HS population translating to the potential for improved health outcomes and the potential for cost offsets to the treatment acquisition costs of imlifidase (for instance if the magnitude of reductions in waiting time enjoyed by the smaller HS population is sufficiently larger than the increase in waiting time suffered by the larger non-HS population) —evidence supporting or quantifying this possibility is not included in the ADAR. The commentary found that the analysis presented in the ADAR is likely to

significantly overestimate population health benefits and underestimate costs associated with providing imlifidase from a healthcare system perspective. However, the commentary also acknowledged the high unmet need in the HS patient population and acknowledged that societal preferences for prioritising difficult-to-transplant patients and those who have spent longer times waiting for a donor kidney should be considered in the decision-making process.

The applicant's pre-ESC response noted that the impact for non-sensitised patients in allocating a kidney to a HS patient is most likely to be a non-substantial delay rather than a denied kidney transplantation. Moreover the pre-ESC response argued that imlifidase may also increase the number of available kidneys through living donation, thereby reducing the numbers of patients on the DD waitlist. However the commentary considered that as long as no DD kidneys are wasted (i.e. there are no patients in the transplant waiting list that could receive an available DD kidney) there is overall no reduction in the requirement for dialysis provision by the healthcare system and therefore cost offsets due to reduced dialysis provision are unlikely to be achieved. While it is acknowledged that there is the potential for cost offsets to be generated through changes in behaviour with respect to living donors, the commentary reiterated that no evidence for this was presented in the ADAR and the overall impact of these elements on costs to the health system in Australia remain unknown.

Transplant rates under current care

The assessment group found that the ADAR's approach for estimating the probability of receiving a transplant in this patient population significantly underestimates the true transplant rate in this population. The ADAR argues that transplant rates in the cPRA ≥95% population and the total ANZKX population converge in 5–6 years, based on ANKX data. As such, these rates in the overall patient population reflect the HS patient population considered in the economic evaluation. This is then extrapolated to the wider DD waitlist population from years 4 to 5, resulting in an estimated transplant rate of approximately 5% per year. However, ANZKX data presented in the ADAR show that even patients with cPRA ≥95% are significantly more likely to receive transplants in earlier years, with 19.6% of HS patients receiving a transplant in year 2. It is unclear why this trend would not also be observed in patients on the DD waiting list. The ADAR presents no data to justify this assumption. Underestimation of the probability of receiving a transplant for patients under current care in the absence of imlifidase will overestimate the incremental benefit of treatment with imlifidase.

Treatment efficacy, graft survival and mortality

Efficacy of imlifidase in the economic evaluation is based on the pooled safety population of 54 patients from the clinical trial program. In this population, 2 patients did not receive a full dose of imlifidase (due to infusion-related reactions) and were therefore not successfully converted to crossmatch negative, leading to a model base case efficacy of 96.3% successful conversion following treatment with imlifidase. One additional patient had a residual positive crossmatch; however, this was deemed clinically insignificant and the patient was subsequently transplanted successfully. As such, the commentary agreed with the base case efficacy estimate of 96.3% used in the ADAR.

Patient survival with a functioning graft and death-censored graft survival were estimated based on parametric survival analysis of clinical trial data. Parametric models were fit for the patient population undergoing a kidney transplant. The ADAR explored different parametric distributions including exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma distributions as candidates. The commentary agreed that parametric survival analysis is an appropriate method to generate extrapolations from the clinical trial data and the appropriate

candidate distributions. Patient survival with a functioning graft and graft survival were all modelled in the base case presented in the ADAR using an exponential distribution. This was justified in the ADAR based on the minimisation of Akaike information criterion (AIC) and Bayesian information criterion (BIC). While goodness of fit to the observed data is an important consideration in the model-fitting process, the economic evaluation is sensitive to extrapolation of the clinical trial data. Limited evidence is presented in the ADAR to justify the choice of parametric distribution based on expectations in clinical practice and validation to registry data. This is especially important given the properties of the exponential distribution, which assume a constant event rate that lacks clinical face validity with respect to patient and graft survival. Furthermore, contrary to expectations, extrapolations of patient risk of death with a functioning graft are lower than population life tables. This suggests that parametric model predictions may significantly underestimate the risk of death in patients with a functioning graft, consequently overestimating the benefits of treatment with imlifidase (Figure 2). Even with a functioning graft, increased survival in this patient population compared with Australian general population estimates does not have clinical face validity.

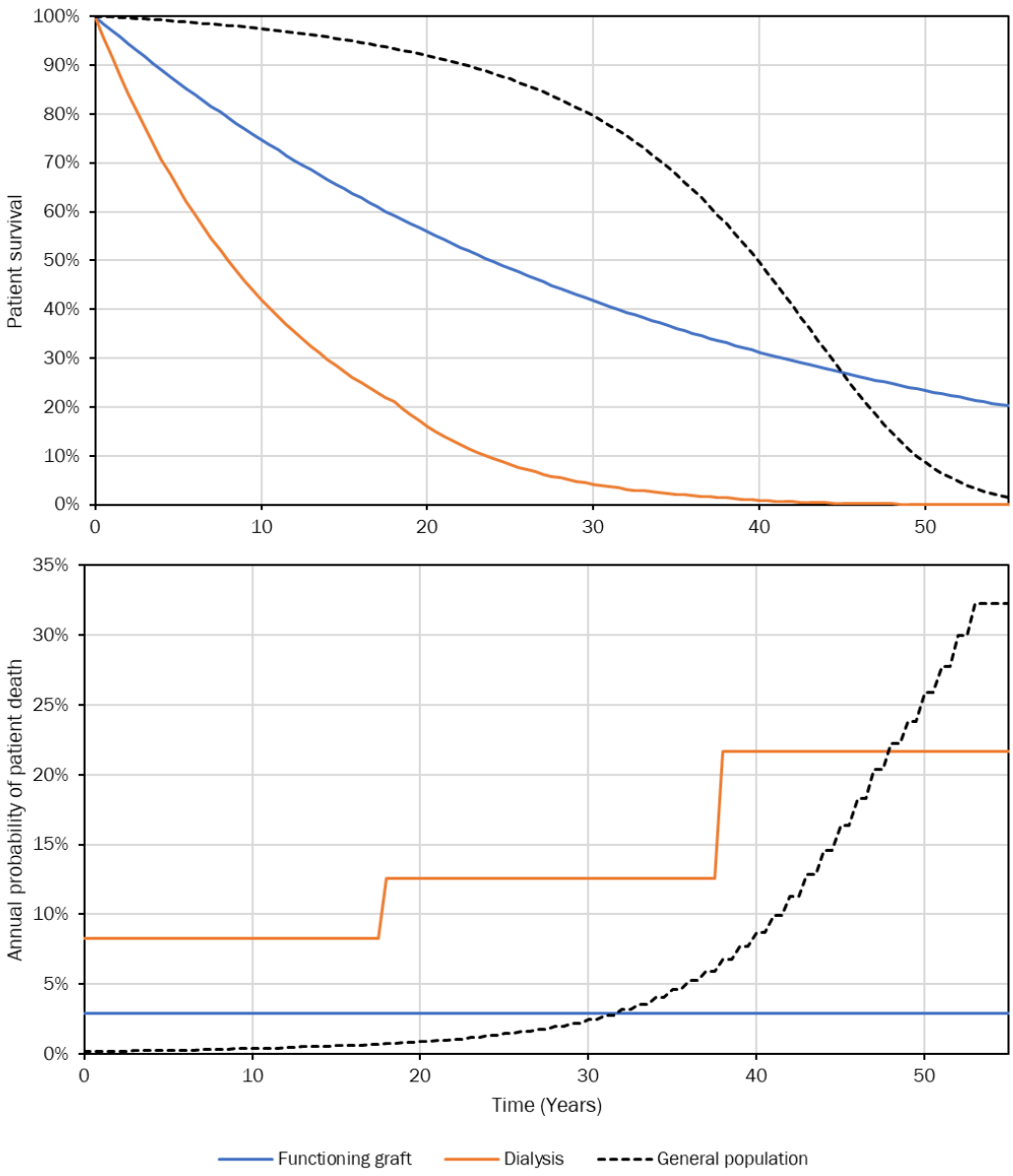

Figure 2: Probability of patient survival (top) and annual probability of patient death (bottom) for patients with a functioning graft, patients undergoing dialysis, and an age- and gender-matched Australian general population.

More generally, the ADAR provides insufficient validation of model extrapolations to clinical practice in Australia, with no validation against observed patient survival with a functioning graft or graft survival in Australia. This is of particular concern in the context of the naïve ITC that has been conducted to demonstrate comparative effectiveness of imlifidase in comparison with current care. There is a high risk of bias resulting from differences in observed and unobserved prognostic and treatment effect modifying variables between patients enrolled in the imlifidase trial program and HS patients in Australia. Given this risk of bias and the resulting uncertainty, it is also unclear why the ADAR has not estimated patient survival and graft survival based on Australian registry data. Although such an approach has the potential to overestimate patient and graft survival, given the more complex needs of the modelled patient population, it would be more plausible than the assumption adopted in the submission (i.e. that patient and graft survival are described by parametric models with exponential distributions). This approach would also address the high risk of bias resulting from the naïve ITC used to estimate comparative efficacy in the HS patient population.

Health-related quality of life

The commentary considered the use of age- and gender-dependent utilities adjusted with a health state utility decrement to be appropriate. However, the ADAR failed to provide information on the target literature search that was conducted to identify utility values for implementation in the model. The commentary considered that this added material uncertainty to the cost-effectiveness estimates. Furthermore, the ADAR provides no discussion on the health-related quality of life (HRQoL) data collected in the 17-HMedIdeS-14 long-term study. Utility values from this study are reported in the clinical study report however, they were estimated using a Danish value set and are thus inappropriate for this analysis. Given the paucity of utility data in the PICO-relevant population, HRQoL data from the 17-HMedIdeS-14 long-term study may provide relevant insights into the relative impact on quality of life for the HS vs non-HS population.

The ADAR notes that no studies were identified by the systematic literature review (SLR) of HRQoL pertaining to the PICO-relevant population, yet 2 papers identified through a targeted literature search were used to inform the disutility values used in the model. The research question posed for the SLR on HRQoL was defined by the ADAR as: *What evidence is available that quantifies HRQoL in HS adult CKD patients awaiting transplant and those who subsequently receive a kidney transplant?* Although the commentary considered the SLR by Cooper et al., 2020[8] to be of good quality, it is highly plausible that the targeted literature search may have led to the omission of relevant evidence. The possibility of study selection bias cannot be discounted. The ADAR used results from the Cooper et al., 2020 SLR, which do not align with the PICO relevant population, in their base case. The commentary believe that the ADAR should have conducted a SLR on HRQoL with relaxed inclusion criteria to identify HRQoL in all transplant patients, which would have captured the SLR conducted by Cooper et al., 2020.

The ADAR does not apply any reduction in HRQoL associated with treatment emergent AEs. The commentary stated that this should be included in the model.

The commentary agreed with the ADAR that it is important to consider the HRQoL impact on carers. The scenario analysis presented in the ADAR has a small impact on the incremental cost-effectiveness ratio (ICER) (approximate reduction of $600 per quality-adjusted life year [QALY]).

[8] Cooper, J.T., et al. (2020). 'Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review.' *Health and Quality of Life Outcomes* 18(1): 310.

Model adverse events

The inclusion and application of AEs in the analysis are appropriate and reasonable.

However, the commentary considered that a reduction in HRQoL associated with treatment emergent AEs should have been modelled, in line with the inclusion of AE healthcare costs.

Model healthcare resource use and costs

In general, the commentary found that the healthcare resource use and costs were applied appropriately.

The main driver of costs is the treatment cost of imlifidase, applied as a weighted cost of the number of vials and dose. The cost of a single Luminex test was included in the base case; increasing this to 2 doses has a small impact on the ICER (approximate increase of $150/QALY).

For transplant and dialysis costs, there is a material impact on the ICER when choosing between the ADAR's micro-costing approach (ICER of [redacted]/QALY) and Kidney Health Australia's estimated costs for 2008–2009 (ICER of [redacted]/QALY). On balance, the Kidney Health Australia (KHA) dialysis costs adjusted for inflation are cheaper and transplant costs more expensive compared with the ADAR's micro-costing approach.

The main driver of the difference between the transplant costs relates to transplant maintenance costs. The inflation-adjusted KHA costs equate to a total of $19,998 compared with a total of $2,877 estimated in the micro-costing approach. The commentary agreed with the ADAR's conclusion that aspects of the KHA study are not well described, making it difficult to determine the generalisability and applicability to current practice. However, the ADAR's micro-costing approach considers that post-transplant reviews incur only the cost of a nephrologist visit ($81.05 as per MBS item 116). The commentary noted that a further exploration of the difference between the KHA estimates and the micro-costing approach with clinical experts to better understand any additional costs incurred during post-transplant follow-up would have been appropriate. The commentary concluded that it is likely the true cost of transplant maintenance falls between the ADAR's micro-costing approach and the KHA estimates.

For the cost of dialysis, the commentary agreed with the use of the ADAR's micro-costing approach. However, the commentary noted the considerable impact that variation in the cost of dialysis has on the ICER, and took the broader perspective that cost offsets estimated by the ADAR are unlikely to be realised in the context of scarce kidney supply.

The commentary generally considered that the costs and resource use associated with AEs in the analysis are appropriate and reasonable. The commentary queried the ADAR's estimation of AE costs but also noted that this has a non-material impact on the ICER.

Incremental costs and effectiveness

The lifetime ICER for treatment with imlifidase, estimated by the ADAR and presented in the submission, was [redacted] QALY (Table 6).

Table 6: Results of the economic analysis

Outcome	Current care	Imlifidase	Incremental
Costs	$724,730	[redacted]	[redacted]
LYs gained	7.65	11.92	4.27
QALYs gained	5.18	9.69	4.51
ICER ($/QALY)	$[redacted]/QALY		

Abbreviations:
ICER = incremental cost-effectiveness ratio, **LY** = life year, **QALY** = quality-adjusted life year
Source:
Table 78 of ADAR

The results of the economic analysis should be interpreted in the context of wider uncertainty around the introduction of imlifidase. The ADAR included a range of scenario analyses in the submission, assessing the sensitivity of model results to changes in assumptions and model parameters. The model was sensitive to the population used to estimate graft and patient survival, as well as the parametric distribution used. Results were also highly sensitive to the approach used to estimate transplant- and dialysis-related costs, as well as excluding the impact of completed chains and the benefits seen in co-transplanted patients. The results of scenario analyses presented by the ADAR are shown in Table 7.

Table 7: Results of scenario analyses

Variable or assumption	Base case value	Scenario value	ICER ($/QALY)	ICER (%)
Base case			[redacted]	
Scenario analyses presented in the ADAR				
Time horizon	Lifetime	10 years	[redacted]	120.1%
Time horizon	Lifetime	20 years	[redacted]	-11.4%
Discounting rates	5.0%	3.5%	[redacted]	-35.4%
Discounting rates	5.0%	0.0%	[redacted]	-70.7%
AMR-DGF population	All imlifidase	UTT-A	[redacted]	0.4%
AMR excluding subclinical	Subclinical included	Subclinical excluded	[redacted]	-1.7%
Graft survival population	All imlifidase	UTT-A	[redacted]	-39.0%
Graft survival distribution	Exponential	Weibull	[redacted]	-38.5%
Survival with a functioning graft population	All imlifidase	UTT-A	[redacted]	-28.8%
Survival with a functioning graft distribution	Exponential	Weibull	[redacted]	8.5%
Dialysis costing	Micro-costing	KHA 2010	[redacted]	77.1%
Dialysis costing	Micro-costing	Gorham 2019	[redacted]	71.8%
Dialysis costing	Micro-costing	Remote location	[redacted]	Became dominant
Transplant costing	Micro-costing	Modified KHA 2010	[redacted]	29.9%
Utility	Cooper 2020	Liem 2008	[redacted]	-7.2%
Add caregiver disutility	No caregiver disutility	Add caregiver disutility	[redacted]	-3.1%

Variable or assumption	Base case value	Scenario value	ICER ($/QALY)	ICER (%)
Excluding co-transplant patients	Including co-transplants	Excluding co-transplants	[redacted]	235.7%
ANZKX transplant rate distribution	Weibull	Exponential	[redacted]	-27.7%
Additional scenario analyses conducted by the assessment group				
ANZKX transplant rate	Estimated from years 5-6 on transplant waiting list	Estimated from years 2-6 on transplant waiting list	[redacted]	77.6%
Costs considered	Considers additional costs of transplant and dialysis cost offsets	Includes additional costs associated with imlifidase administration only	[redacted]	506.1%
Patients in LD chain requiring imlifidase to receive a transplant	No other patients in LD chain require imlifidase	One other patient requires imlifidase	[redacted]	99.2%
Graft survival distribution	Exponential	Generalised gamma	[redacted]	77.6%

Abbreviations:
KHA = Kidney health Australia 2010, **LY** = life-year, **QALY** = quality-adjusted life-year, **ICER** = incremental cost effectiveness ratio, **AMR** = antibody-mediated rejection, **DGF** = delayed graft function, **ANZKX** = Australia and New Zealand kidney exchange, **UTT-A** = unlikely to be transplanted–agnostic.
Source:
Table 80 of ADAR

In addition to the scenarios presented in the submission, the commentary found there are other areas of significant uncertainty with the potential to have a material impact on the estimated cost-effectiveness of imlifidase. A summary of the key uncertainties and drivers in the economic model are summarised in Table 8, along with a description of the anticipated impact, and, where possible, the results of additional scenario analyses conducted by the assessment group as part of the commentary.

In its pre-ESC response the applicant proposed an alternative ICER value of $[redacted] per QALY gained based on correcting an error in the costing of immunosuppressive treatment and excluding all spill-over effects (both positive and negative) i.e. the scenario captured in the value of $[redacted] in Table 7 but with a corrected cost of immunosuppressive treatment.

Table 8: Exploration of key uncertainties and drivers of the model

Description	Rationale and method	Impact
Bias resulting from a naïve ITC between imlifidase and current care	The economic evaluation is based on comparative efficacy estimates derived from a naïve ITC. There are material differences in patient characteristics between imlifidase clinical trials and the Australian patient population. There is also the potential for further unobserved differences in prognostic factors that should be considered in assessing bias in an unanchored naive ITC.	Potential large impact on economic evaluation given the impact on efficacy estimates and outcomes in the modelled patient population. It is uncertain if any bias would favour the intervention or current care.
Underestimation of current care transplant rate	Based on ANZKX transplant data presented by the ADAR, the assumed value of 5% is likely underestimated when compared with transplant rates in earlier years. Estimating transplant rates from year 2 in ANZKX onwards aligned to PICO inclusion results in an estimate of 12.8% per year vs 5% in company base case.	Large impact in favour of the intervention. Scenario analysis using the average transplant rate from ANZKX over years 2–6 resulted in an ICER of [redacted]/QALY.
Costs and benefits considering donor kidneys as a scarce resource – negative spill-over	The economic evaluation presented by the ADAR does not consider the negative impact of providing a scarce donor kidney to an HS patient rather than another potential recipient on the waiting list. As such, estimated cost offsets associated with reductions in dialysis provision are unlikely to be realised by the healthcare system in Australia. Similarly, benefits in health outcomes are achieved as a result of the availability of a donor kidney, rather than treatment with imlifidase, and as per the submission, HS patients are likely to experience poorer health outcomes than non-HS patients.	Large impact in favour of the intervention. Scenario analysis excluding cost offsets associated with dialysis and costs associated with transplant result in an ICER of [redacted]/QALY. Consideration of the potential for negative population health outcomes associated with transplanting HS patients would result in imlifidase being dominated by current care.
Inclusion of other HS patients requiring treatment with imlifidase in LD chains	The economic evaluation does not consider the potential for other patients in LD chains to require treatment with imlifidase to complete the chain. There is no justification provided by the ADAR to support this assumption.	Large impact in favour of the intervention. One additional patient requiring imlifidase to close an LD chain results in an ICER of [redacted]/QALY.
HS patients not joining LD chains after introduction of imlifidase	If HS patients are able to receive transplants from a crossmatch-positive LD, it is unclear if patients will join LD chains following the introduction of imlifidase.	Large impact in favour of the intervention. Assuming patients will no longer join LD chains results in an ICER of [redacted]/QALY.
Overestimation of patient and graft survival	Model extrapolations of graft survival and patient survival with a functioning graft assume a constant event rate, lacking clinical face validity. Although the ADAR presents other parametric distributions as part of scenario analyses, they are all likely to overestimate patient survival with a functioning graft. The most conservative model predictions of survival with a functioning graft do not have clinical face validity in comparison with Australian general population estimates, with model predictions of mortality risk being overtaken by risk of mortality in the general population. No validation has been presented by the ADAR demonstrating that model predictions are aligned with registry data in Australia.	Potentially large impact, likely to favour the intervention. Overestimation of graft survival and patient survival with a functioning graft will result in increased benefits in patients treated with imlifidase. Distribution resulting in poorer graft survival than the model base case (generalised gamma) results in an ICER of [redacted]/QALY. The impact of poorer survival with a functioning graft cannot be explored in the current model, so the impact is uncertain.

Abbreviations:
ANZKX = Australian and New Zealand Kidney Exchange, **HS** = highly sensitised, **ICER** = incremental cost-effectiveness ratio, **ITC** = indirect treatment comparison, **LD** = living donor, **PICO** = population intervention comparator outcomes, QALY = quality-adjusted life year

14. Financial/budgetary impacts

The net financial impact of imlifidase on state and federal governments is summarised in Table 9.

The commentary agreed that the method of analysing both prevalent and incident data in the forward estimates is a suitable approach, particularly considering the anticipated significant impact of introducing imlifidase on the current and projected patient population's steady state. However, the ADAR's approach of solely considering the financial impact on patients expected to use imlifidase, rather than presenting the entire patient cohort, results in an incomplete assessment of the net financial impact of introducing imlifidase.

Table 9: Net financial impact

Parameter		2024	2025	2026	2027	2028	2029
Number of people eligible for imlifidase	Deceased donor	170	155	138	114	88	64
	Living donor	30	27	24	20	15	10
	Total	200	182	162	134	103	74
Number of people who receive imlifidase	Deceased donor						
	Living donor						
	Total						
Cost of imlifidase to all governments							
Change in use of dialysis-related costs							
Net financial impact to state and federal governments							

The ADAR projects annual budget savings of $ million by 2029, driven by dialysis-related cost-savings that are unlikely to be realised due to the introduction of imlifidase. The commentary found that this analysis does not consider that there are more patients on the transplant waiting list than donor kidneys available. As such, if a patient could not receive a kidney due to sensitisation, another patient would likely receive this kidney instead and the costs of dialysis would be avoided regardless of the introduction of imlifidase. Therefore, the commentary preferred that no cost offsets be considered in the financial impact of imlifidase, resulting in an average budget impact of approximately more than $ million per year over 2024- 2029.

The only scenario where the introduction of imlifidase could result in financial cost-savings for the full patient cohort is one in which imlifidase-treated patients on the LD waiting list close paired kidney chains that would otherwise remain open. The ADAR has not fully explored this scenario, and given that it is a smaller patient group, the potential cost-savings may not be significant enough to offset the overall financial impact across the entire patient population. In addition, the introduction of imlifidase will likely reduce the number of HS patients joining the LD waiting list, thus further reducing the potential cost offset imlifidase could provide by closing paired kidney chains.

The commentary found that the ADAR has made assumptions to determine the net financial impact that lack scientific rigour and transparency, making the presented net financial impact highly uncertain.

The commentary noted that the ADAR does not include additional administration/monitoring costs, such as potentially prolonged cold ischemia time or the cost of patients who are initiated with imlifidase but do not proceed to transplantation (clinical trial data shows that

52/54 patients given a full dose of imlifidase proceeded to transplantation). In addition, there is a lack of justification for several assumptions made by the ADAR, such as the estimate of annual LD grafts, the number of new HS patients per year, rate of transplantation of HS patients in the absence of imlifidase, length of chain for transplants and projected market uptake.

The commentary noted that the health economic evaluation estimated an increase in total costs following introduction of imlifidase though the financial analysis estimates cost savings by 2029. However the pre-ESC response clarified that the differences comes from the difference in the nature of these models: the Cost Effectiveness Model (CEM) is a cohort model and therefore follows the same patients from model entry to death. The Financial Impact Model (FIM) accounts for the annual number of patients to be treated and allows for inflows and outflows of patients every year. The assessment group accepted this clarification.

15. Equity considerations

The commentary concurred with the ADAR that equity considerations are pertinent to using imlifidase in HS patients. Notably, pregnancy is a significant factor contributing to sensitisation, putting women, particularly mothers, at a higher risk of being highly sensitised and potentially facing disadvantages in accessing kidney transplantation. The commentary agreed that employing imlifidase would help promote equity between genders and among women with and without history of pregnancy.

The commentary observed that certain patient groups, such as Aboriginal and Torres Strait Islander patients and other ethnic minorities, are more likely to be highly sensitised and remain on waiting lists for extended periods, with minimal prospects for transplantation. This also raises equity concerns. The commentary concurred with the ADAR that employing imlifidase helps to achieve a more equitable allocation of kidneys for Aboriginal and Torres Strait Islander patients and those within other minority ethnic groups.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- There is limited and uncertain evidence regarding the comparative efficacy and safety of imlifidase. The evidence is strongest for short-term efficacy outcomes in achieving successful transplantation.
- There is uncertainty about the long-term outcomes of imlifidase treatment. Further data may be forthcoming from follow up of initial trials, new Phase III trials, and real-world experience from the UK and Europe (where imlifidase has conditional marketing approval with further data to be provided to regulators in 2023 and 2025 for use in deceased donor (DD) kidney transplants).
- While there is a clinical unmet need for highly sensitised patients to be able to receive donor kidneys and move off dialysis, there is uncertainty about the likely uptake in practice as highlighted by submissions from state and territory governments. The Transplant Society of Australia and New Zealand and OrganMatch may be helpful in clarifying the unmet need and practicalities about how imlifidase could be implemented into clinical practice. Consider soliciting submissions from other states and territories who are yet to provide input (Queensland, NT, ACT, Tasmania).

Economic issues:

- There is uncertainty around the inputs used for the economic model. The key data for imlifidase (such as graft survival and survival rates) are based on parametric extrapolations of the pooled clinical trial data, which includes the all-transplanted population (this population also includes those who received imlifidase but would not have been eligible for imlifidase treatment under the proposed PICO criteria) and the unlikely to be transplanted – agnostic to source of donor kidney (UTT-A) population (only those who meet the PICO criteria) who may be more appropriate for the economic evaluation. There is also uncertainty around the probability of transplant without imlifidase, which is likely underestimated. Regarding the current care inputs, there are concerns around the heterogeneity between populations, which makes comparisons subject to confounding.
- The main limitations associated with the observed incremental clinical benefits in the model-based evaluation are the quality of the imlifidase trials (no control arm, small sample size, lack of long-term data to reasonably inform the long-term effectiveness of the treatment) and the uncertainty in the indirect comparison.
- The base case ICER heavily relied on several uncertain assumptions in the economic model. In particular the model assumes that for every patient transplanted with a living donor (LD) kidney following imlifidase treatment, six other LD-waitlisted patients would also be transplanted via the creation of a donation chain for co-transplant patients. It also estimates cost offsets in the intervention arm due to reduced dialysis in the target highly sensitised (HS) population but ignores the potential impact of opportunity costs of kidneys denied to the non-HS population (both in terms of dialysis costs and incremental outcomes in that population) due to earlier access to donor kidneys for the HS population with a fixed size deceased donor kidney pool. Omitting cost offsets associated with reductions in the provision of dialysis to the HS population increases the ICER from $[redacted] to $[redacted] per QALY gained.

Financial issues:

- The financial impacts, with estimated cost savings by year 6, are uncertain. The estimated cost savings are driven by dialysis-related cost savings, which may be overestimated due to uncertainty in the uptake rate and the likelihood of dialysis-related cost savings not being fully realised by the Australian healthcare system.

Other relevant information:

- There are implementation challenges to consider. Addressing the significant implementation challenges will require working with multiple stakeholders, while further modelling and evidence may help define potential positive equity impacts and potential negative utility impacts for Australians on transplant waitlists.
- There are also ethical issues. A key ethical issue to consider with this application is the equity versus utility trade-off: (i) On the one hand, imlifidase may increase equity in access to transplantation for HS patients who otherwise may be unlikely to undergo transplantation; these include people who need re-transplantation, people who have been pregnant and First Nations people; (ii) On the other hand, because DD kidney numbers are already fully utilised and imlifidase does not result in a net increase in DD kidney transplantations, more non-sensitised patients would remain on the DD waitlist and on dialysis if there is increased access to DD transplantations for HS patients. There may also be poorer incremental outcomes associated with kidney transplants to the HS population. Therefore overall the increased access to DD transplantations for HS patients facilitated by imlifidase may result in a possible decreased overall utility for the population.
- In the absence of better data and studies, there is a potential role for a risk-sharing agreement, price reduction and full review of clinical effectiveness, cost-effectiveness and budget impact analysis when longer-term data become available in the event that imlifidase is approved for funding.

ESC discussion

ESC noted that this application from Hansa Biopharma was requesting funding for the use of imlifidase for the desensitisation of highly sensitised (HS) adult kidney transplant patients with a positive crossmatch against an available deceased donor (DD) or living donor (LD) who are unlikely to be transplanted under current kidney allocation systems. Funding is sought through the National Health Reform Agreement (NHRA) Addendum 2020–25 for highly specialised therapies.

ESC noted that, subject to a positive recommendation from MSAC, funding agreements will need to be negotiated with each respective state and territory.

ESC noted that an application to register imlifidase was submitted to the Therapeutic Goods Administration (TGA) but was still under consideration. ESC noted that the application was for provisional registration, and as such provision of updated clinical trial evidence will be a condition of provisional regulatory approval.

ESC noted that imlifidase is a high-cost drug; one vial costs approximately $[redacted], and most patients require two vials considered as one dose. A small proportion (estimated to be 6.5% in the ADAR, based on clinical trials data) of patients require two doses (a cost of approximately $[redacted]) because they do not achieve a crossmatch conversion; this can potentially increase the cold ischaemic time (with an additional crossmatch test) and may add an additional 8–10 hours to the transplant process. As such, guidance from the National Institute for Health and Care Excellence (NICE) limits imlifidase to one infusion. However, ESC noted that PASC agreed that imlifidase should not be limited to one dose, although PASC noted that it should be specified that, if given, the second dose would be in the context of the initial transplant. ESC also noted that guidance from NICE limits imlifidase to DD kidney transplant recipients.

ESC noted that a kidney transplant is the preferred treatment option for patients with end-stage kidney disease (ESKD), with patient survival and quality of life post-transplantation being superior to dialysis. However, around one-third of patients waiting for kidney transplantation have donor-specific antibodies (DSA) against human leukocyte antigens (HLA) which may present a significant immunologic barrier to transplantation.

ESC noted that recent amendments to the Australian prioritisation algorithm (introduced May 2021) to prioritise HS patients to receive donor kidneys are anticipated to improve access to transplantation for HS patients. However, these patients are still likely to have less access to transplantation than non-sensitised patients. Therefore, there is a clinical need for an effective desensitisation treatment for HS ESKD patients with a positive crossmatch against an available DD or LD.

ESC noted that input was received from four state and territory governments: [redacted]. These submissions expressed concern regarding the level and quality of evidence provided, especially the short length of follow-up, small sample size and relevance to the Australian context. They also noted that the following should be considered:

- mechanisms for ongoing data collection and the need for post-implementation review
- the price of treatment should be lower and should include the cost of tissue typing
- eligibility criteria
- kidney allocation algorithm
- the need to limit treatment to specialised treatment centres with specialised trained staff

- impact of imlifidase on access to transplantations for non-HS patients
- equity considerations.

The submissions also noted that only a small number of patients may be eligible for imlifidase. Specifically, [redacted]

ESC noted that there were further submissions received from a consumer group, transplant unit and professional individuals. These submissions stated that imlifidase treatment will increase equity of access to transplantation for HS patients (but that it would need to be made available to all transplant units and for all HS patients), will improve quality of life and longevity, and could result in future cost savings due to decreased dialysis. However, consultation did note that, if transplantation was not successful in HS patients, it would result in someone else missing out on a donor kidney. The need for long-term monitoring was also noted in the feedback, which would be an additional expense.

ESC noted that the proposed eligible population are adult patients with EKSD who are HS and unlikely to be transplanted. Additionally, they must:

- be active on the DD and/or LD waitlist
- have a calculated panel-reactive antibody (cPRA) test of ≥95%
- have a positive crossmatch against an available donor
- have been on the donor transplant list for at least one year.

ESC noted that the comparator was current care, which is the absence of imlifidase and includes remaining on the transplant list and receiving ongoing dialysis until a transplant becomes available, which may or may not occur. If a transplant does become available, it will be at a decreased rate compared to the intervention. ESC noted that the comparator does not include other available off-label desensitisation treatments for LD transplantations. These were not considered an appropriate comparator for the PICO as they are not often offered to patients given their low transplantation success rate (with only a small sub-population expected to respond).

ESC noted that the clinical evidence for the intervention was primarily based on four small Phase II clinical studies of imlifidase. ESC noted that the trial data used for the intervention were from single-arm uncontrolled studies conducted in small, heterogenous populations. Also, in some instances, the other medications used in the trial were not routinely used in Australian practice, which made the generalisability of the trial results to Australian practice uncertain. ESC noted the applicant comment that they are conducting a Phase III post-approval efficacy study. The commentary also identified a possible second Phase III study, and suggested that these two studies could help address evidence gaps and uncertainties when the results become available.

ESC noted that comparator outcomes were sourced from published Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) kidney replacement therapy outcomes data (from the 44th annual report, published in 2021). ESC noted that, because direct comparative imlifidase studies could not be conducted, the applicant used naïve indirect treatment comparison (ITC) to indirectly compare a relevant subpopulation of patients from the imlifidase studies with the comparator. The applicant assessed the risk of bias of their ITC to be moderate. However, ESC noted that the applicant used the Risk Of Bias In Non-randomised Studies – of Interventions

(ROBINS-I) tool to evaluate the risk of bias for both the intervention and comparator studies. However, ESC questioned the use of ROBINS-I in evaluating individual single arm trials of the intervention, ESC considered that ROBINS-I could only be used to evaluate the applicant's naïve indirect comparison, which likely has a high risk of bias as it does not try to emulate a target trial (for example, through inverse probability of censoring weighting). ESC noted that this assessment aligned with the commentary which also assessed the ITC as likely having high risk of bias.

ESC noted that the imlifidase clinical data were reported for three populations: unlikely to be transplanted – agnostic to source of donor kidney (UTT-A) which is all patients who meet the PICO criteria, inclusive of both LD and DD transplant lists, unlikely to be transplanted (UTT) which is the subset of the PICO defined patients only on the DD transplant list, and all transplanted which is all imlifidase-enabled patients across all studies including those who would not have been eligible for imlifidase under the PICO criteria.

Regarding comparative safety, ESC noted that, out of 54 patients (from all studies):

- one patient did not receive a transplant following an infusion-related reaction (serious adverse event) with imlifidase that resulted in treatment and study discontinuation
- one patient experienced graft failure and decided to not complete the study
- one patient who was not transplanted in the first study was transplanted in a later study.

Regarding comparative effectiveness, ESC noted that

- all patients (albeit a small group) showed crossmatch conversion; although it appeared that that one patient had not converted, this was deemed to be clinically insignificant, and transplantation went ahead.
- all UTT and UTT-A patients had cPRA ≥95% and were transplanted. In the absence of imlifidase, it was estimated that 24 of the 25 UTT patients (96%) had <1% compatible donors in the Eurotransplant database. ESC noted that the applicant stated that Australian data would be similar, but the commentary argued that it may not be; for example, 43.6% of patients on the Australian DD waitlist with cPRA 95–98% are transplanted in the first year.

ESC noted that patient survival was good up until six months after imlifidase treatment and transplantation. ESC noted that while three patients died between 6–12 months, to the knowledge of the applicant, there is no reason to assume that any death was related to imlifidase treatment, or due to kidney malfunction. The applicant also stated that the survival estimates were applicable to an Australian population based on overall survival in transplant patients in Australia being better than the US and similar to Sweden (the two countries where almost all the trial participants were based). The commentary agreed that it is reasonable to apply these results to an Australian population.

Regarding graft survival, ESC noted that, in the all-transplanted patients, three (7%) patients lost their grafts during the six-month study period. The commentary agreed with the applicant that the results were applicable to the Australian population, based on graft survival in transplant patients in Australia being better than the US (where most trial patients were).

Regarding graft rejection over time due to antibody-mediated rejection (AMR), ESC noted that AMRs were reported in 10 patients in the UTT-A and UTT populations, and all were successfully treated using standard therapies. ESC noted that the applicant considered this to be a safety consideration rather than an efficacy outcome. Imlifidase aims to avoid hyperacute rejection and is not expected to impact other rejection events. ESC noted that the commentary accepted that rates of AMR from the UTT-A subgroup (30%) were broadly consistent with the variable frequency of HS patients reported by the European Medicines Agency (12–61%); however, it was still unclear how generalisable these data are to an Australian population.

ESC noted that the applicant reported that kidney function (by glomerular filtration rate) was "satisfactory" at six months for most patients. However, the commentary noted that the definition of "satisfactory kidney function" was unclear. For delayed graft function (DGF), ESC noted that the applicant stated that the incidence of DGF can vary greatly among centres, from 3.2% to 63.3%. The applicant stated that one US study found that the duration of DGF, rather than the occurrence of DGF, was associated with graft survival, and the applicant cited expert opinion that the duration of DGF was shorter in Australia than the US (where most of the trial participants were). However, no justification was provided for this.

ESC noted that health-related quality of life (HRQoL) was not collected in the trials. ESC noted that both the five-level European Quality of Life (EQ-5D-5L) and the short-form Kidney Disease Quality of Life Questionnaire (KDWOL-SF 1.3) improved over time in participants, but data were available for only a few patients.

ESC noted the clinical claim that the use of imlifidase results in superior effectiveness and at least non-inferior safety compared with current care in the absence of imlifidase. ESC noted that the commentary considered that the efficacy evidence sufficiently supported the superior-effectiveness claim. However, ESC considered there was uncertainty in comparative effectiveness and the applicability of the evidence to the Australian HS treatment population, with small patient numbers and a high risk of bias. ESC also considered the claim of at least non-inferior safety to be uncertain. Both the applicant-developed assessment report (ADAR) and the commentary noted that assessing the adverse effect profile is difficult, given that patients in both arms experienced adverse events of different types and frequencies. Moreover, obtaining long-term data on graft survival can be challenging, as it requires ongoing monitoring of patients over many years and may be subject to various confounding factors. ESC noted that the applicant is conducting a Phase 3 Post Approval Efficacy Study and the commentary identified a possible second Phase 3 study. ESC noted the commentary's view that these two studies could help address evidence gaps and uncertainties.

ESC noted that the economic evaluation was a model-based cost-utility analysis (CUA) using a lifetime time horizon (initial age of 47 years) and a Markov model with four health states. ESC noted that in the model, graft survival and the transition from dialysis to functioning graft (hence leading to the avoidance of dialysis costs for the HS population) is what drives the outcomes in determining the incremental cost effectiveness ratio.

ESC considered the model structure (health states included in the model) to be appropriate. The model included the possibility of not converting all patients into negative crossmatch after imlifidase (not all patients receive a transplant), the possibility of transplant in the comparator arm, and a health state "dialysis – not waitlisted" that allows some patients who are no longer fit for transplant to be removed from the transplant lists. However, the base case ICER heavily relied on several uncertain assumptions in the model:

- The model assumed that, for every patient transplanted with an LD following imlifidase treatment, six other LD-waitlisted patients would also be transplanted; this was based on expert opinion and assumes the creation of a donation chain for co-transplant patients.
- The model was designed to estimate cost offsets in the intervention arm due to reduced dialysis, but it ignores the potential impact of opportunity costs (in favour of the proposed intervention). Kidneys are scarce resources, with demand that exceeds supply; any kidney used with imlifidase could have potentially been used for patients outside of the target population (on the transplant waitlist), with cost savings from avoiding dialysis.
- The model considered the impacts on incremental health outcomes – that is, considering benefits for HS patients treated with imlifidase (transition to the functioning graft state), but did not consider the incremental outcomes associated with providing the donor kidney to another patient on the waitlist.

ESC noted that these uncertainties and in particular the one relating to the potential impact of opportunity costs are not typically discussed in an economic evaluation but are of relevance here because of the inability of the supply of donor kidneys to match demand.

ESC considered that, without further evidence and analysis, the potential impact of these model structuring issues and assumptions on the ICER was unclear but potentially may lead to an underestimated ICER (as discussed further below). ESC noted that the kidney allocation scenario in the economic model could be conceptualised as a 'queuing' problem in the sense that with or without imlifidase, there would always be patients queueing for a kidney (though there would be a shorter queueing time for HS patients) without a significant expansion in the supply of donor kidneys.

ESC noted that, for the model inputs for imlifidase, key data (such as graft survival and survival rates) came from parametric extrapolations of the pooled clinical trial data. The data from the all-transplanted population (n=46 patients), included patients with a cPRA <95% (28% of patients) or a negative crossmatch (15%) who would not be eligible for imlifidase treatment in accordance with the PICO. ESC considered that the UTT-A population (n=30 patients) was the closest match to the target population, so, although a smaller group than the all-transplanted population, would be the most appropriate for use in the economic evaluation. ESC considered the main limitations associated with the observed incremental clinical benefits in the model-based evaluation were the quality of the imlifidase trials and the uncertainty in the indirect comparison.

ESC also considered there to be uncertainty around the probability of transplant without imlifidase – this was estimated to be 5% based on clinician expert opinion, but ESC considered this to likely be an underestimate (in favour of the intervention) as a higher rate of HS patients are transplanted through the Australia and New Zealand Paired Kidney Exchange (for instance 19.6% of HS patients in year 2 according to the commentary). Regarding the current care inputs, ESC was concerned about the heterogeneity between populations, which makes comparisons subject to confounding.

ESC noted that the utility values were sourced from the age- and gender-dependent health utilities (EQ-5D-5L) in a randomly selected community sample in South Australia (adjusted with utility decrements). The commentary noted that the health state utility decrement values used in the model were derived from a targeted literature review and not adequately justified. However, ESC acknowledged that the utility values did not have a big impact on the ICER.

ESC noted that the main driver of incremental cost in the economic model was the total cost of imlifidase, based on a weighted cost of the number of vials (per kilogram) and number of doses ($[redacted]), plus the cost of prior Luminex testing and co-medication ($[redacted]/patient/lifetime).

ESC noted that the base case ICER was $[redacted] per quality-adjusted life year (QALY) gained. ESC noted that the submission conducted a range of deterministic sensitivity analyses. The variables with the biggest impact on the ICER were the number of co-transplants in a donation chain when imlifidase is used, and the cost of dialysis (i.e. the micro costing approach compared to using Kidney Health Australia inflation adjusted costs).

ESC considered that, because of the substantial uncertainty around the model inputs and assumptions, a relatively conservative approach should be used in the base-case analysis. ESC considered the following conservative approaches and their effect on the ICER:

- Using a higher probability of transplant without imlifidase (based on the average transplant rate from the Australia and New Zealand Paired Kidney Exchange over years 2–6) results in an ICER of $[redacted] per QALY gained.

- Excluding the assumption that for every patient transplanted with an LD following imlifidase treatment, there would be six other LD-waitlisted co-transplant patients results in an ICER of $[redacted] per QALY gained.
- Adjusting for both these variables results in an ICER of $[redacted] per QALY gained.
- Using the UTT-A population and also adjusting for all variables in the economic analysis results in an ICER of $[redacted] per QALY gained.

ESC also noted that omitting cost offsets associated with reductions in the provision of dialysis facilitated by imlifidase (for the reasons discussed previously i.e. because of the opportunity costs to the non-HS population) results in an ICER of $[redacted] per QALY gained.

ESC noted that an epidemiological approach was used to determine financial impacts. The net financial impact in the ADAR ranged from a cost of $[redacted] million in year 1 to a saving of $[redacted] million in year 6, which was driven by dialysis-related cost savings. ESC considered that this may be an overestimate due to uncertainty in the uptake rate and the likelihood of dialysis-related cost savings not being fully realised by the Australian healthcare system. ESC noted that, if cost savings were not realised, the average budget impact would be approximately $[redacted]/year from 2024 to 2029.

ESC considered that, in the absence of better data and studies, there was a potential role for a risk-sharing agreement, price reduction and full review of clinical effectiveness, cost-effectiveness and budget impact when longer-term data become available. ESC noted that, in the pre-ESC response, the applicant discussed a plan for long-term studies to monitor graft survival.

ESC considered that there were also several implementation issues. The eligibility criteria and the DD kidney allocation algorithm would need to be updated by the Renal Transplant Advisory Committee (RTAC) of the Transplantation Society of Australia and New Zealand (TSANZ) if imlifidase is supported, and this will require time and consultation. There is also a need to consider the availability of trained specialists, specialised treatment centres and other specialised services, including rapid provision and reporting of donor-specific antibody testing, which is provided by Lifeblood. Based on expert opinion from the ADAR, only seven transplant centres are currently able to undertake desensitisation. Finally, there is a need to establish mechanisms for ongoing data collection both pre and post implementation, potentially through ANZDATA.

ESC also noted that there were several ethical issues to consider with this application and in particular the equity versus utility trade-off:

- On the one hand, imlifidase may increase equity in access to transplantation for HS patients who otherwise may be unlikely to undergo transplantation; these include people who need re-transplantation, people who have been pregnant and First Nations people.
- On the other hand, as already noted in the context of the economic modelling, because DD kidney numbers are already fully utilised and imlifidase does not result in a net increase in DD kidney transplantations, more non-sensitised patients would remain on the DD waitlist and on dialysis if there is increased access to DD transplantations for HS patients. There may also be poorer incremental outcomes associated with kidney transplants to the HS population. Therefore overall the increased access to DD transplantations for HS patients facilitated by imlifidase may result in a possible decreased overall utility for the population. The state and territory submissions agree; New South Wales and Victoria noted the risk of organ rejection due to immune recovery, while South Australia and Western Australia noted that increased cold ischaemic time (especially if two infusions are needed) may lead to poorer outcomes. The pre-ESC response stated that the impact for non-sensitised patients in allocating a kidney to a HS patient is most likely to be a non-substantial delay, not a denied kidney transplantation,

and that imlifidase enabled kidney transplantation for HS patients who demonstrate graft survival outcomes similar to other patient populations routinely transplanted.

ESC therefore considered that the intervention would be more impactful if there was a surplus of kidneys, and the only way to increase supply was through the LD pool, which would require targeted campaigns. However, data were uncertain for LDs, and patients on LD waitlists had other treatment options.

17. Applicant comments on MSAC's Public Summary Document

There is a clinical unmet need for highly sensitised Australian patients to be able to receive donor kidneys and move off dialysis. Kidney Transplant Specialists were supportive of this application, making Idefirix available to those unable to be transplanted despite being on the waiting list substantially longer than patients who are not highly sensitised. Current kidney organ allocation in Australia balances equity of access with the potential utility of the organ for most patients. However, some patients that are highly sensitised are still left with no option and remain on dialysis which has significant impact on patients' morbidity, mortality and quality of life. Imlifidase helps enable equity of access to the standard of care, kidney transplantation, to a small number of highly sensitised patients identified within the eligibility criteria of the ratified PICO population agreed by the PICO Advisory Sub Committee (PASC). The applicant contends Imlifidase is a cost-effective treatment for the specific population receiving an imlifidase enabled transplantation. If clinical decision making for kidney organ allocation was aligned with MSAC preferred model scenarios focussed on spill-over effects, higher risk patients such as the diabetics and older patients would seldom be transplanted, which would challenge equity principles established by the Australian organ allocation system. Hansa Biopharma remains aligned with the conclusions of the PASC within the ratified PICO "*PASC agreed [that as such these] off-label desensitisation regimens were not an appropriate comparator for imlifidase".* Hansa Biopharma remains fully committed to continue engaging with MSAC and the Australian transplant community to ensure Australian patients have public funding for Idefirix.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website