Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Idefirix

Active ingredient: Imlifidase

Sponsor: Hansa Biopharma

May 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
AMR	Antibody-mediated rejection
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
BCR	B-cell receptor
BMI	Body mass index
CDC	Complement-dependent cytotoxicity
CDCXM	Complement-dependent cytotoxicity cross match
CKD	Chronic kidney disease
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
cPRA	Calculated panel reactive antibody
CV	Coefficient of variation
CXM	Cross match
DLP	Data lock point
DSA	Donor specific antibody
ESRD	End-stage renal disease
EU	European Union
FCXM	Flow cytometry cross match
HLA	Human leukocyte antigen
HUT	Highly unlikely to be transplanted
IgG	Immunoglobulin G
IVIg	Intravenous immunoglobulin
MFI	Mean fluorescence intensity
PD	Pharmacodynamic(s)
Ph. Eur	European Pharmacopoeia
PI	Product Information
PK	Pharmacokinetic(s)
PRA	Panel reactive antibody

Abbreviation	Meaning
PSUR	Periodic safety update report
RMP	Risk management plan
SAB	Single antigen bead
SAE	Serious adverse event
scIgG	Single chain IgG
t½	Half life
TEAE	Treatment related adverse event
TGA	Therapeutic Goods Administration
Vc	Central volume of distribution
Vp	Volume of distribution
Vz	Volume of distribution

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Idefirix
Active ingredient:	Imlifidase
Decision:	Approved for provisional registration
Date of decision:	7 July 2023
Date of entry onto ARTG:	10 July 2023
ARTG number:	391413
, *Black Triangle Scheme*	Yes
for the current submission:	As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	Hansa Biopharma (Australia) Pty Ltd Level 19, 181 William Street, Melbourne
Dose form:	Powder for concentrate for solution for infusion
Strength:	11 mg
Container:	Vial
Pack size:	1 or 2 vials
Approved therapeutic use for the current submission:	*Idefirix has **provisional** approval 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 (see Section 5.1 Pharmacodynamic properties, Clinical trials). The use of Idefirix should be reserved for patients who are otherwise unlikely to receive a kidney transplant.* *The decision to approve this medicine has been made based on limited data. More comprehensive evidence is required to be submitted.*
Route of administration:	Intravenous infusion
Dosage:	Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of sensitised renal transplant patients. The dose is based on patient body weight (kg). The recommended dose is 0.25 mg/kg administered as a single dose preferably within 24 hours before transplantation. One dose is adequate for crossmatch conversion in the majority of patients

	but, if needed, a second dose can be administered within 24 hours after the first dose. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	Category B2 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Hansa Biopharma (Australia) Pty Ltd (the sponsor) to register Idefirix (imlifidase) 11 mg, powder for concentrate for solution for infusion, vial for the following proposed indication:[1]

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

Renal failure requiring renal replacement therapy is an important cause of morbidity and mortality in Australia. In Australia in 2020, 27,684 patients received renal replacement therapy (overall prevalence of 1078 per one million). In 2020, 885 renal transplants were performed (34 per one million) of which 181 were living donor transplants.

Sensitisation to human leukocyte antigens (HLA) is a barrier to renal transplantation due of a greatly increased risk of graft rejection. The degree of sensitisation is typically measured using a panel of T-cell lymphocytes representing the donor population using a complement-dependent cytotoxicity (CDC) assay to determine the donor pool proportion to which the transplant candidate is expected to be CDC cross-match incompatible. Highly sensitised patients are less likely to receive a transplant due to difficulties in finding a suitably matched donor. 'Highly sensitised' is defined as a calculated panel reactive antibody (cPRA) value of at least 80% and includes up to 28% of patients on the transplantation waitlist.

There is a further relevant subgroup of patients who were considered to be highly unlikely to be transplanted without imlifidase treatment (for example, associated with unsuccessful

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

desensitisation, or highly unlikely effective desensitisation). This patient group may not have had an opportunity to be seriously considered for a transplant due to the reduced likelihood of success.

The sponsor used the following three criteria to identify highly unlikely to be transplanted (HUT) patients:

- Calculated panel reactive antibody of at least 95% based on a mean fluorescence intensity (MFI) cut-off of 3000, or a historical peak PRA of at least 95%.
- Deceased and living donor transplantation.
- Positive cross match (CXM) (determined by CDC (CDCXM) or flow cytometry cross match (FCXM test) towards the available graft immediately prior to imlifidase treatment and transplantation.

This group is likely to be the main target population for imlifidase. In the Phase II clinical trial program, 30 out of the 46 transplanted patients were classified as HUT patients. Compared to the general transplant population, they typically suffer from risk factors for shorter graft survival.

The current management options include (alone or in combination according to the local standard of care): plasma exchange, intravenous immunoglobulin (IVIg), anti-CD20 antibodies (for example, rituximab), complement blockers (for example, eculizumab), or waiting for a more immunologically compatible organ offer.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

This product received orphan drug designation on 9 May 2022 for the following indication:

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

At the time the TGA considered this submission, a similar submission had been approved in European Union (EU) on 25 August 2020, United Kingdom on 25 August 2020 (National license 1 January 2021, exit from EU), Israel on 21 March 2022 and Switzerland on 6 May 2022.

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union (EU)	5 February 2019	Approved on 25 August 2020	*Idefirix is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients*
United Kingdom	5 February 2019	Approved on 1 January 2021 (national license: due to exit from EU)	*Idefirix is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.*
Israel	5 July 2021	Approved on 21 March 2022	*Idefirix is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.*

Region	Submission date	Status	Approved indications
Switzerland	5 July 2021	Approved on 6 May 2022	*Idefirix can be used before a kidney transplant for rapid and temporary inactivation of immunoglobulin G (IgG) in adult patients with positive crossmatch against an available deceased donor. The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.*

The Delegate noted that the indications in the EU, Switzerland, and Israel are restricted to deceased donors, and do not include living donors.

The Delegate noted that the sponsor has stated that no regulatory agency has refused to approve the product for the proposed indication on safety grounds.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the provisional registration process.

Table 2: Timeline for Submission PM-2022-02499-1-2

Description	Date
Designation (Orphan)	9 May 2022
Determination (Provisional)	9 May 2022
Submission dossier accepted and first round evaluation commenced	1 August 2022
First round evaluation completed	22 December 2022
Sponsor provides responses on questions raised in first round evaluation	28 February 2023
Second round evaluation completed	14 April 2023

Description	Date
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 May 2023
Sponsor's pre-Advisory Committee response	16 May 2023
Advisory Committee meeting	1 and 2 June 2023
Registration decision (Outcome)	7 July 2023
Administrative activities and registration on the ARTG completed	10 July 2023
Number of working days from submission dossier acceptance to registration decision*	189

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Quality

Structure

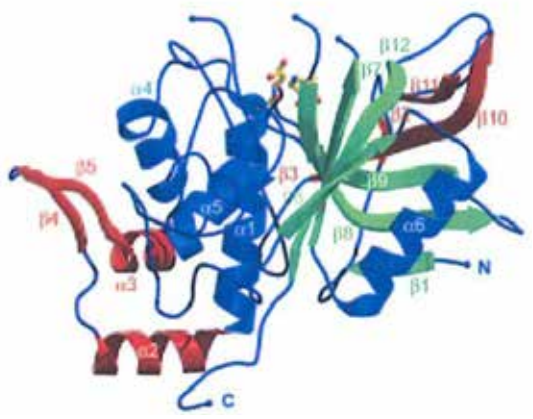
Idefirix consists of the IdeS molecule (imlifidase) based on IdeS gene sequence. Imlifidase is expressed in *Escherichia coli.*

The theoretical molecular mass of imlifidase (35071 Da) is based on the amino acid sequence deduced from the coding DNA sequence. The molecular mass has been verified by mass spectrometry.

Imlifidase does not undergo post-translational modifications, is non-glycosylated and contains no signal peptide.

Imlifidase is a monomeric protein and folded into two distinct domains to form a functional enzyme with a cysteine residue in a catalytic triad at the active site. This cysteine residue is crucial for the activity of imlifidase. The protein structure is shown in Figure 1.

Figure 1: Protein structure of imlifidase.



Drug substance – stability

The real time data submitted support a shelf life of 24 months when stored at -80°C or lower.

Drug product – solution for injection – components/excipients

The drug substance is imlifidase. All excipients are pharmacopeial, non-novel, and are not of human or animal origin . The excipients are mannitol, polysorbate 80, Trometamol (Tris [hydroxymethyl] aminomethane), disodium edetate dihydrate, hydrochloric acid 0.1N and nitrogen.

Drug product – solution for injection – container

The container closure is considered suitable for its intended use as demonstrated by compatibility and stability studies. The Biomaterials and Engineering Section evaluator has no objections to the registration of Idefirix (imlifidase) in relation to container safety.

Drug product – solution for injection – stability

Following evaluation, the recommended storage condition is 18 months when stored at 2 to 8°C.

The recommended shelf life and storage conditions for the opened/reconstituted/diluted product are 24 hours when stored at 2 to 8°C of which up to four hours may be at ambient temperature (25 ± 2°C). The product is not photostable.

Infectious disease safety

Sufficient evidence has been provided to demonstrate that the risks related to adventitious agents in the manufacturing of Idefirix (imlifidase) have been managed to an acceptable level.

Endotoxin evaluation

The sponsor claims that compendial methods according to the referenced monograph were followed, including the Bacterial Endotoxin Test, which references European Pharmacopoeia (Ph. Eur). 2.6.14 & USP <85>.[2] Assay qualification data should also have been provided.

Summary and conclusion

There are no objections on quality grounds to the approval of Idefirix (imlifidase).

The finished product quality control for batch release includes identity, potency, purity, impurities, sterility (Ph. Eur.), bacterial endotoxin (Ph. Eur.) and several other general tests.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the Product Information (PI), Consumer Medicines Information (CMI) and the Australian Register of Therapeutic Goods (ARTG).

Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. From

[2] ICH guideline Q4B Annex 14 to Note for Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Bacterial Endotoxins Tests – General Chapter, available at https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-q4b-annex-14-note-evaluation-recommendation-pharmacopoeial-texts-use-ich-regions_en.pdf

quality perspective, compliance with Therapeutic Goods Legislation and relevant TG Orders as well as consistency with relevant guidelines and the ARGPM has been demonstrated.

Proposed wording for conditions of registration

- Laboratory testing & compliance with Certified Product Details (CPD)
  - i. All batches of Idefirix (imlifidase) supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - ii. When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

  A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website

  [for the form] https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescription-medicines

  [for the CPD guidance] https://www.tga.gov.au/guidance-7-certified-product-details

Nonclinical

The submitted nonclinical dossier was largely in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines (ICH S6).[3] The overall quality of the nonclinical dossier was satisfactory.

In vitro, imlifidase cleaved all human immunoglobulin G (IgG) subclasses (IgG1, IgG2, IgG3 and IgG4) within the nanomolar range. The presence of pre-existing anti-imlifidase antibodies did not appear to significantly alter imlifidase efficacy. *In vivo*, imlifidase cleaved rabbit IgG's within 6 hour to 24 hour post-dose at subclinical doses (based on maximum concentration [C_{max}]), thus, supporting the proposed clinical dosing regimen. Only a small proportion of dog IgG was cleaved by imlifidase into F(ab')2, Fc and single chain IgG (scIgG).

Imlifidase also cleaved IgG-type of B-cell receptor (BCR) with an efficacy comparable to cleavage of IgG in serum. However, the cleaved IgG-BCR is rapidly replaced by an intact IgG-BCR on the cell surface. While the cleavage of IgG-type BCR can result in silencing of memory B-cells, the effect appears to be temporary.

[3] Pre-clinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 [R1]), available at https://www.ema.europa.eu/en/pre-clinical-safety-evaluation-biotechnology-derived-pharmaceuticals-ich-s6-r1

At clinically relevant concentrations, imlifidase cleaves monoclonal and polyclonal antibodies and fusion proteins approved as therapeutics. Thus, the exposures of antibody and fusion protein therapies are likely to be affected adversely by the concurrent administration of imlifidase.

No dedicated safety pharmacology studies were conducted. Cardiovascular and respiratory safety pharmacology endpoints tested in the dog repeat dose toxicity studies revealed no noteworthy findings at doses up to 40-fold clinical exposure (based on C_{max}). Central nervous system effects are not expected given the large molecular weight and hydrophilicity of imlifidase.

The pharmacokinetic profile in rabbits and dogs was sufficiently similar to that of humans despite the low activity of imlifidase to dog IgG. Lower elimination half-life of imlifidase was observed with rabbit and dog cf. human. The distribution volume of imlifidase in humans was broadly comparable to the investigated species. No dedicated metabolism and/or excretion studies were performed, which is acceptable.

Imlifidase had a low order of acute intravenous toxicity in rabbits and dogs.

Repeat-dose toxicity studies by the intravenous route were conducted in rabbit (2- and 4-weeks) and dog (2- and 3-weeks). Target organs for toxicity were the lungs (rabbit: reversible alveolar macrophages and minimal to moderate peri-/arteritis in multiple organs), heart (rabbit: myocardial degeneration with minimal to moderate focal inflammatory cell infiltrations), spleen (rabbit: increased spleen weight and cellularity) and tubular basophilia (dog), with immunotoxicity at least in part, contributing to the observed toxicities. Myocardial degeneration changes were minimal to slight and were not seen after two weekly doses or after four weeks of recovery.

No genotoxicity or carcinogenicity studies were conducted in line with the guidance for a biotechnology-derived pharmaceutical.

No imlifidase-related local tolerance issues were identified with the clinical strength formulation.

Conclusions and recommendations

There are no nonclinical objections to registration.

Pregnancy category

No fertility studies were conducted. While no imlifidase-related adverse histopathological findings were noted in male reproductive organs in repeat-dose toxicity studies in rabbits, hyperaemic uterus and oviducts, and potential bleeding (observed as black spots) in the ovaries was observed in female rabbits dosed daily with imlifidase. No noteworthy changes in embryofetal development parameters were noted in rabbit at subclinical safety exposure margins.

Pregnancy category B2 is appropriate.[4]

[4] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- Two Phase I studies
  - Study 11-HMedIdeS-01
  - Study 18-HMedIdeS-15
- Four Phase II studies
  - Study 13-HMedIdeS-02
  - Study 13-HMedIdeS-03
  - Study 14-HMedIdeS-04
  - Study 15-HMedIdeS-06
- Two follow-on studies:
  - Study 17-HMedIdeS-13
  - Study 17-HMedIdeS-14

Pharmacology

Pharmacokinetics

There were two formulations used in the development program. The pharmacokinetics (PK) profile of imlifidase was similar for the two intravenous formulations (Process 1 and Process 2), but formal bioequivalence testing was not performed.

Absorption

Imlifidase is administered by intravenous infusion. In Study 01, the semi-log plot of plasma concentration versus time indicates a two-compartment model, that is a redistribution phase.

Studies 01 and 15 were conducted in healthy male volunteers. Studies 02, 03, 04, and 06 were conducted in the target population. The PK parameters for the 0.12 mg/kg and 0.24 mg/kg dose levels are summarised in Table 4 (Study 01), and for the 0.24 mg/kg and 0.25 mg/kg doses in Table 5 (all studies with PK data).

Table 3: Study 01. PK parameters of imlifidase after a single IV infusion (0.12 mg/kg and 0.24 mg/kg)

Parameter		0.12 mg/kg (N=4)	0.24 mg/kg (N=3)
C_{max} (µg/mL)	Mean (SD) Median Min: Max	3.14 (0.33) 3.11 2.75:3.57	5.66 (0.61) 5.81 4.98:6.18
T_{max} (h)	Mean (SD) Median Min: Max	0.40 (0.12) 0.34 0.33:0.58	0.39 (0.08) 0.35 0.33:0.48
AUC (h·µg/mL)	Mean (SD) Median Min: Max	126 (43) 122 79:181	225 (108) 172 154:350
$t_{½}$ (h) distribution	Harm. Mean Median Min: Max	4.0 4.2 3.2; 4;7	2.7 2.5 2.3; 3.8
$t_{½}$ (h) elimination	Harm. Mean Median Min: Max	128 147 75:231	107 141 70:154
CL (mL/h/kg)	Mean (SD) Median Min: Max	1.1 (0.4) 1.0 0.7:1.5	1.2 (0.5) 1.4 0.7:1.6
V_{ss} (L/kg)	Mean (SD) Median Min: Max	0.18 (0.06) 0.17 0.14:0.26	0.18 (0.06) 0.14 0.14:0.25
V_z (L/kg)	Mean (SD) Median Min: Max	0.21 (0.07) 0.20 0.15:0.30	0.20 (0.08) 0.16 0.15:0.29

Table 4: Summary of PK parameters of imlifidase after a single IV infusion to healthy men and patients with CKD (0.24 or 0.25 mg/kg)

		Study 01 (5.3.3.1)	Study 15 (5.3.3.1)	Study 02 (5.3.4.2)	Study 03 (5.3.5.2)	Study 04 (5.3.5.2)	Study 06 (5.3.5.2)
		0.24 mg/kg N=3	0.25 mg/kg N=15	0.25 mg/kg N=4	0.25 mg/kg N=5	0.24 mg/kg N=17	0.25 mg/kg N=18
AUC (h×µg/mL)	Geom. mean (%CV)	210 (47)	137 (82)[c]	427 (64)	178 (73)	159 (74)[a]	156 (45)[b]
C_{max} (µg/mL)	Geom. mean (%CV)	5.63 (11)	5.8 (21)	6.33 (16)	5.82 (20)	-	-
$t_{½}$ (h) distribution	Harmonic mean	2.7	1.8[c]	6.3	5.1	4.1[a]	4.6[b]
$t_{½}$ (h) elimination	Harmonic mean	107	89[d]	89	74	71[a]	76[b]
CL (mL/h/kg)	Geom. mean (%CV)	1.1 (47)	1.8 (82)[c]	0.6 (64)	1.4 (73)	1.5 (74)[a]	1.6 (45)[b]
V_z (L/kg)	Geom. mean (%CV)	0.19 (38)	0.20 (67)[c]	0.09 (20)	0.15 (53)	0.17 (74)[a]	0.19 (27)[b]

[a]N=14
[b]N=9
[c]N=13
[d]N=12

Distribution

Healthy volunteers: In Study 01, the semi-log plot of plasma concentration versus time indicates a two-compartment model, that is a redistribution phase. The geometric mean (%CV) volume of distribution (Vz) was 0.19 (38) L/kg. In Study 15, following an intravenous dose of 0.25 mg/kg, the geometric mean (%CV) Vz was 0.20 (67%) L/kg.

Target group: In the target population, geometric mean (%CV) Vz values were 0.09 (20) L/kg (Study 02), 0.15 (53) L/kg (Study 03), 0.17 (74) L/kg (Study 04) and 0.19 (27) L/kg (Study 06).

Metabolism

The Delegate noted that no metabolism studies were submitted.

Excretion and elimination

Distribution half-life (t½; harmonic mean): 2.7 hours (Study 01), 1.8 hours (Study 15).

Elimination t½ (harmonic mean): 107 (70 to 153) hours (Study 01), 89 (7 to 238) hours (Study 15), 89 (49 to 297) hours (Study 02), 74 (52 to 94) hours (Study 03 - 0.25 mg/kg group), and 93 (49 to 171) hours (Study 03 - 0.50 mg/kg group).

Mean (arithmetic) (standard deviation) clearance: 1.1 (0.38) mL/kg/h (Study 01), 0.86 (0.39) mL/h/kg (Study 02), 1.68 (1.18) mL/h/kg (Study 03 - 0.25 mg/kg group), 1.21 (0.76) mL/h/kg (Study 03 - 0.50 mg/kg group), and 1.75 (0.81) mL/h/kg (Study 06).

Geometric mean (coefficient of variation [CV%]) clearance: 1.8 (82%) mL/h/kg (Study 15), and 1.5 (94%) mL/h/kg (Study 4).

Dose proportionality

Healthy volunteers: In Study 01, exposure were dose-proportional in the dose range 0.010 to 0.24 mg/kg.

Target group: In Study 03, exposure were dose proportional in the dose range studied.

Accumulation

The Delegate noted that no mass balance studies were submitted.

Target population

The PK parameters in the healthy volunteers were similar to those in patients prior, and undergoing, renal transplantation.

Population pharmacokinetics

Source: Clinical pharmacokinetic data from Phase I Studies 01 and 15, and Phase II Studies 02, 03, 04 and 06 provided the source data for a population pharmacokinetic and PK/pharmacodynamics (PD) modelling of imlifidase (27 healthy subjects and 52 patients with chronic kidney disease (CKD) with 734 PK and 810 PD observations).

Methods: Imlifidase and IgG concentration-time data were analysed using non-linear mixed effects modelling with residual variability and inter-individual variability models. Specific covariates with a potential impact on imlifidase PK were examined: pre-existing anti-drug antibody (ADA) concentration, study related differences, and patient weight.

Results: Imlifidase PK in both healthy subjects and patients with CKD were well described by a two compartments model, with linear elimination and a proportional residual error model.

Estimates included a clearance of 0.0976 L/h (CV = 48%), central volume of distribution (Vc) of 3.5 L (CV = 24%), intercompartmental clearance of 0.179 L/h (CV = 52%), and peripheral volume of distribution (Vp) of 6.1 L (CV = 93%). Inter-individual variability was estimated as independent random effects, except for a significant covariance between CL and Vp (CV = 54%).

In the final model (Run 330), the estimated exponent for the following significant covariate relationships were:

- Pre-dose ADA relationship with clearance: –0.158 (decreased clearance with higher pre-dose ADA)
- Body weight relationship with Vc: 0.427 (increased Vc with higher body weight)

However, the population PK/PD modelling did not suggest a clinically significant effect between pre-dose ADA levels and the PD effect of imlifidase at the proposed dose.

Pharmacodynamics

Mechanism of action

Imlifidase is a cysteine protease derived from the IgG-degrading enzyme of *Streptococcus pyogenes* that cleaves the heavy chains of all human IgG subclasses but no other immunoglobulins.

Primary pharmacodynamic effects

Intravenous imlifidase administration induced rapid IgG cleavage in healthy males and in the CKD target population (Table 6). The maximum effect on IgG concentration was reached within six hours in Studies 02 and 03, and within 24 hours in Studies 04 and 06. The small amounts of IgG detected typically constituted scIgG. The depletion of IgG was reversible (not all recovered to pre-transplant levels; see time course description below), and the IgG levels started to increase 4 to 7 days after administration of 0.24/0.25 mg/kg.

Table 5: Percentage reduction of IgG plus single chain IgG from Baseline by time in response to a single intravenous infusion of imlifidase to healthy subjects and patients with chronic kidney disease

Time	Study 01 (5.3.3.1)	Study 15 (5.3.3.1)	Study 02 (5.3.4.2)	Study 03 (5.3.5.2)	Study 04 (5.3.5.2)	Study 06 (5.3.5.2)
	0.24 mg/kg N=4 Mean(SD)	0.25 mg/kg N=15 Mean(SD)	0.25 mg/kg N=4[a] Mean(SD)	0.25 mg/kg N=5 Mean(SD)	0.24 mg/kg N=15 Mean(SD)	0.25 mg/kg N=18[b] Mean(SD)
Baseline	0	0	0	0	0	0
1 hour	73 (4)	95 (3)	66 (14)	81 (6)	51 (27)	-
2 hours	89 (2)	98 (1)	92 (6)	95 (3)	-	85 (14)
4 hours	-	99 (0)	95 (6)	98 (2)	-	-
6 hours	94 (2)	99 (0)	98 (2)	98 (2)	89 (9)	93 (8)
8 hours	-	99 (1)	98 (2)	98 (1)	-	-
24 hours	94 (2)	98 (2)	>99 (0)	99 (1)	94 (6)	95 (5)
2 days	93 (3)	96 (2)	-	>99 (0)	-	93 (7)
3 days	-	94 (8)	-	99 (2)	-	-
4 days	91 (5)	92 (9)	-	-	-	-
7 days	82 (9)	86 (12)	-	95 (3)	80 (36)	92 (7)
14 days	51 (38)	40 (32)	-	85 (12)	-	-
21 days	40 (37)	28 (27)	-	69 (23)	-	-
28 days	37 (36)	22 (27)	-	63 28)	-	-
63 days	26 (25)	3 (29)	-	43 (25)	-	-

[a]First dose only

[b]3 subjects received 2 doses 12-20 hours apart

Secondary pharmacodynamic effects

In Study 01, there was no long-term effect on anti-tetanus IgG or anti-CMV IgG. The MFI from the CD19 positive cells stained for F(ab')2 (that is IgG-BCR) was reduced both by the 0.12 mg/kg and the 0.24 mg/kg dose levels. All the volunteers gradually regained $CD19^+$ cells with an intact BCR during follow up.

Time course of pharmacodynamic effects

In Study 01, the maximal effect was achieved 2 to 6 hours after dosing in all four volunteers. F(ab')2 and Fc were at the lowest concentrations between one and seven days after dosing. IgG concentrations were beginning to recover 1 to 2 weeks after dosing.

In Study 03, in patients undergoing renal transplant, time to recovery of IgG was analysed in four patients. The six other patients did not have recovery of IgG to pre-transplant levels. In two patients in the 0.25 mg/kg group the time to recovery was 122 days and 160 days. In two patients in the 0.5 mg/kg group, time to recovery was 22 days and 63 days. The median (range) time to 80% recovery of single antigen bead-HLA antibodies was 68 (29 to 181) days in the 0.25 mg/kg group and 15 (8 to 62) days in the 0.5 mg/kg group.

The PD of imlifidase has been adequately characterised in the proposed usage. This has been explored at different dose levels and the time course of effect has been described.

Dosage selection for the pivotal studies

A dose range from 0.12 mg/kg to 0.5 mg/kg was explored. The response was inadequate at the 0.12 mg/kg dose level, but adequate in the 0.25 mg/kg to 0.5 mg/kg dose range. There was no clinically significant response difference between the 0.25 mg/kg and 0.50 mg/kg dose levels. The proposed dosing and administration are to administer 0.25 mg/kg as a single dose and then

confirm cross-match conversion from positive to negative before transplantation. If necessary, a second dose of 0.25 mg/kg can be administered within 24 hours. This proposed dosing regimen is supported by the data submitted in the dossier.

Efficacy

There were five completed studies with efficacy data, four Phase II studies and one follow-on study. The four Phase II studies were:

- Study 06 (15-HMedIdeS-06) (main Phase II study)
- Study 04 (14-HMedIdeS-04) (main supportive Phase II study)
- Study 03 (13-HMedIdeS-03) (safety and dose-finding study with efficacy endpoints)
- Study 02 (13-HMedIdeS-02) (safety and dose-finding study with efficacy endpoints)

Additional supportive data were provided from the following:

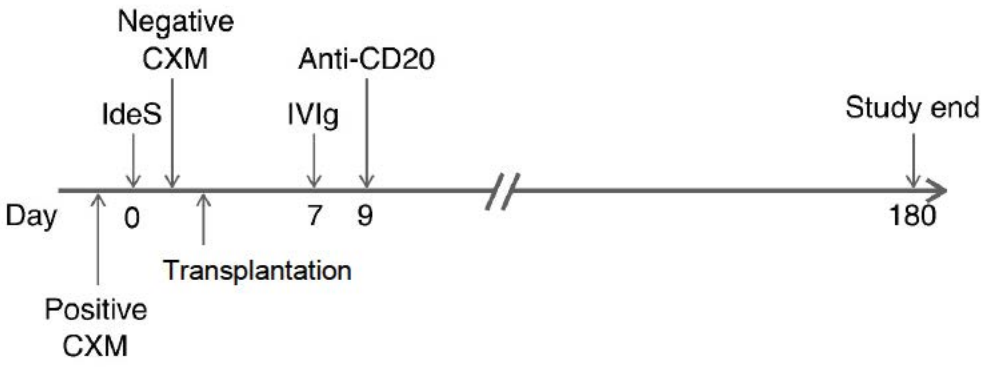
- Study 13 (17-HMedIdeS-13) (retrospective follow-on study with patients from Studies 02 and 03)
- Study 14 (17-HMedIdeS-14) (ongoing follow-on study with patients from Studies 02, 03, 04, and 06)

Study 06 (15-HMedIdeS-06)

Study 06 is an open-label, single arm (no comparator), multicentre Phase II study to evaluate the efficacy of imlifidase prior to renal transplantation in 19 adult men and women (aged 18 to 70 years of age) with a positive CXM test. The study was conducted from September 2016 to July 2018 at five sites in three countries.

The primary efficacy objective was to assess the efficacy of imlifidase in creating a negative CXM test. The other objectives were to assess other efficacy, safety, PK, and PD objectives.

Figure 2: Study 06. Study design schema



Inclusion criteria includes male or female aged 18 to 70 years at the time of screening; patients on the kidney transplant waiting list who had previously undergone desensitisation unsuccessfully or in whom effective desensitisation was highly unlikely. Patients in Sweden required an anti-HLA antibody status with panel reactive antibody (PRA) of at least 80%; patients in France required a donor specific antibody (DSA) with a MFI value of at least 3000 and a positive cross-match.

Exclusion criteria included previous treatment with imlifidase, or high dose IVIg treatment (2 g/kg body weight) within 28 days prior to imlifidase treatment; lactating or pregnant

females; HIV-positive patients; patients who had a live donor and tested positive for ImmunoCAP anti-imlifidase IgE.

Treatments include imlifidase 0.25 mg/kg administered by intravenous infusion over 15 minutes, as a single dose, but if considered safe and the desired effect was not achieved (negative CXM test) after the first dose, an additional dose could be given within two days.

Prior to imlifidase administration, the patients were pre-treated with glucocorticoids and antihistamines. In addition, the patients were treated with IVIg (on Days 6 to 8), rituximab (anti-CD20 antibody, nine days after imlifidase), prophylactic antibiotics, immunosuppressing agents and, if indicated, with anti-thymocyte globulin derived from horse or alemtuzumab (anti-CD52 antibody).

Baseline characteristics: 21 patients were screened, 19 included in the study, with 16 completing the study. 3 patients withdrew: one due to AE, one withdrew themselves and one due to 'other' reason. Baseline patient demographics and disease characteristics are shown in Table 10.

Magnitude of the treatment effect and its clinical significance

Primary efficacy endpoint: Proportion of patients converting from a positive CXM to a negative CXM within 24 hours after imlifidase dosing (met if at least one assay was positive at pre-dose and the last assay within 24 hours post-dose was negative) (Table 7 and Table 8).

17 out of 19 patients (89.5%) (full analysis set) converted from a positive to a negative CXM, while 2 out of 19 patients (10.5%) did not.

Table 6: Study 06 Primary endpoint: summary of cross match response (full analysis set)

Conversion within 24 hours	N=19 n (%)
Yes	17 (89.5)
No	2 (10.5)

Source: modified from EOT Table 14.1.16
N=Number of patients in FAS; n=number of patients with data

Table 7: Study 06 Primary endpoint: Flow cytometry cross match and complement-dependent cytotoxicity cross match pre-dose and 24 hours post-dose (full analysis set)

	FCXM N=18					CDCXM N=12				
	Predose		Postdose			Predose		Postdose		
	T+	T-	T+	T-		T+	T-	T+	T-	T missing
B+	5	12	0	0	B +	2	6	0	0	0
B-	0	0	1[a]	17	B -	0	2	0	2	5
B missing	1	0	0	0	B missing		2	0	2	3

[a]Borderline flow crossmatch but negative virtual crossmatch – judged as not clinically significant

Secondary endpoints include:

- Donor specific antibodies:
  - All patients had at least one HLA mismatch DSA at Baseline (highest number for an individual patient: 12 mismatches). 17 out of 18 patients had at least one DSA with MFI > 3000 at pre-dose.
  - After dosing DSAs declined rapidly, reaching the lowest level at between 6 and 96 hours and started to increase again at Day 3 to 14.

  - 11 patients had all DSAs < 3000 MFI after 2 hours of dosing, 4 patients after 6 hours, one patient at hour 48, one patient at hour 96, and one at Day 90.

- Time to negative CDC and flow cytometry CXM tests: could not be calculated due to missing time data.
- Kidney function (up to 180 days post treatment):
  - 16 out of 18 transplant patients had a functional kidney at the end of the study and were not dependent on dialysis.
  - Regarding patients with a functional kidney after 6 months:
    - 4 out of 16 had an eGFR > 60 mL/min/1.73 m^2
    - 11 out of 16 had an eGFR of 30 - 59 mL/min/1.73 m^2
    - 2 out of 16 had an eGFR of < 30 mL/min/1.73 m^2

Study 04 (14-HMedIdeS-04)

Study 04 is an open label, single arm (no comparator), single centre Phase I/II study to evaluate efficacy, safety and tolerability of imlifidase prior to renal transplantation in 17 adult men and women (aged 18 to 70 years of age) with end-stage renal disease (ESRD) and a positive CXM test. This 180-days study was conducted from June 2015 to June 2017 at one site.

Primary efficacy objective includes assessment of the efficacy of imlifidase in eliminating DSAs in DSA- and flow cytometry CMX positive, highly sensitised patients.

Other objectives include other efficacy, safety, PK, and PD objectives.

Table 8: Study 04 design schema

Screening From signing informed consent to Day 0	**Treatment period** **Days 1-7**	**Observation period** **Days 8-28**	**Follow up End of trial** **Day 180**
Eligibility	IMP administration Transplantation Observation and assessments	Observation and assessments	Follow-up assessments

Inclusion criteria includes male or female aged 18 to 70 years at the time of screening; end-stage renal disease awaiting transplantation on the UNOS list; no known contraindications for therapy with IVIg 10%, rituximab, plasmapheresis or imlifidase; cPRA > 50% demonstrated on three consecutive samples, patient highly-HLA sensitized and a candidate for deceased donor transplantation after desensitisation; at transplant, patient must have a donor-specific DSA/CMX+ non-HLA identical donor; pre-transplant vaccination with *Streptococcus pneumoniae* and *Neisseria meningitides*.

Exclusion criteria included the use of IVIg within seven days prior to planned imlifidase administration; use of investigational agents within four weeks of participation; recipients of extended criteria donors or living donors.

Treatments: Imlifidase 0.24 mg/kg, administered by IV infusion over 15 minutes, as a single dose (no second dose).

Non-investigational treatments: Premedication: methylprednisolone 40 mg intravenously, acetaminophen 650 mg orally, diphenhydramine 150 mg orally. Prophylaxis: intravenous ganciclovir (while inpatient) and valganciclovir (while outpatient) for six months, fluconazole 100 mg daily for one month for fungal prophylaxis, trimethoprim 80 mg and sulfamethoxazole 400 mg daily for 12 months for *Pneumocystis jirovecii* pneumonia and bacterial prophylaxis. Patients received prophylactic antibiotics (ciprofloxacin) and alemtuzumab (Campath) 30 mg 4 days post-transplant. In addition, high dose corticosteroids was administered on Days 1-4, and IVIg 7 to 14 days post-transplant.

Baseline characteristics: 17 patients were included in the study and 15 (88%) completed. One patient withdrew and one was lost to follow-up. Baseline patient demographics and disease characteristics are shown in Table 10.

Table 9: Studies 02, 03, 04, and 06. Demographics and baseline characteristics of transplanted patients

Characteristics	Study 02 N=1	Study 03 N=10	Study 04 N=17	Study 06 N=18	All N=46
Age (years)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
<35	0 (0)	2 (20)	6 (35)	5 (28)	13 (28)
35 - 49	0 (0)	1 (10)	5 (30)	11 (61)	17 (37)
50 - 64	1 (100)	5 (50)	6 (35)	2 (11)	14 (31)
>64	0 (0)	2 (20)	0 (0)	0 (0)	2 (4)
Sex	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male	1 (100)	3 (30)	8 (47)	13 (72)	25 (54)
Female	0 (0)	7 (70)	9 (53)	5 (28)	21 (46)
Race	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Caucasian	1 (100)	9 (90)	14 (82)	11 (61)	35 (76)
Asian	0 (0)	1 (10)	2 (12)	1(6)	4 (9)
Black	0 (0)	0 (0)	0 (0)	4 (22)	4 (9)
Other	0 (0)	0 (0)	1 (6)	2 (11)	3 (6)
Historical transplantations (n)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
0	0 (0)	6 (60)	6 35)	2 (11)	14 (31)
1	1 (100)	4 (40)	9 (53)	9 (50)	22 (48)
2	0 (0)	0 (0)	2 (12)	5 (28)	8 (17)
3	0 (0)	0 (0)	0 (0)	2 (11)	2 (4)
Total time on dialysis (years)					
Median	2.5	2.1	5.4	5.3	4.9
cPRA (%) (MFI cut-off >3000)					
Median	42.00	67.02	97.82	99.41	97.45
Living donor	0	2	0	5	7
Deceased donor	1	8	17	13	39
Previous attempts of desensitization (n)	0	0	14	5	19

Source: Module 5.3.5.3; Table 1.3.2, Table 1.3.5, Table 1.3.7
N=total number of patients; n=number of patients with observation
Study 02 and Study 03 were conducted in Sweden, where desensitization programs do not currently exist
cPRA: Anti-HLA analyzed by central reading by Hansa Biopharma AB, Lund, Sweden. Calculated using the cPRA calculator hosted by OPTN (UNet^{SM} computer system) (cut-off >2000 MFI)

Magnitude of the treatment effect and its clinical significance

Primary efficacy endpoints include:

- Donor specific antibodies:
  - DSAs were defined as antibodies directed against donor HLA measured in the single antigen bead (SAB)-HLA assay and with an MFI value > 2000.
  - All the MFI values decreased at 6 and 24 hours post-dose and were < 2000 in all except one patient.
- Incidence of allograft rejections:
  - One patient suffered a hyperacute antibody-mediated rejection of the kidney, which was considered as being IgM and/or IgA mediated. No intact IgG was detected at the time of the rejection.
- Kidney function (up to 180 days follow-up):
  - Renal function improved significantly post-transplant, except in the patient with the graft rejection. At end of study, 9 (56%) patients had an eGFR ≥ 60 mL/min/1.73 m^2, 6 (38%) had 30 to 59 mL/min/1.73 m^2, and one < 30 mL/min/1.73 m^2.
  - Proteinuria (generally mild to moderate) was observed in 77% of the patients one week after treatment and transplantation, but decreased subsequently and affected three (19%) of the patients one month after transplantation.
- Renal biopsy evaluation (at Day 180): suffering from missing data (9 out of 17 missing)
  - Signs of active antibody mediated rejection in one (6%) patient and signs of subclinical active antibody mediated rejection in one other (6%) patient.

Study 03 (13-HMedIdeS-03)

Study 03 is an open label, single arm (no comparator), ascending dose, dose finding Phase II study to evaluate safety, tolerability, efficacy and PK of imlifidase in renal transplantation in 10 adult men and women (aged 18 years or above) with CKD with dialysis and relevant antibodies.

The study was conducted at two sites in Sweden from June 2015 to October 2016.

Primary objective includes evaluation of safety and tolerability of imlifidase until six months after dosing.

Main efficacy objective is to find an imlifidase dose which in the majority of the patients resulted in HLA antibody levels acceptable for transplantation, within 24 hours from dosing.

Other objectives include other efficacy, safety, PK, and PD objectives.

Inclusion criteria included age 18 years or above; CKD and in dialysis with preformed anti-HLA antibodies (non-DSA, DSA or both), negative T-CDC CXM and at least one antibody MFI > 3000; Available blood type ABO-compatible donor (living or deceased donor).

Exclusion criteria included patients who had received cell transplantation or cell therapy within 5 years prior to imlifidase dosing; Patients treated with biological therapies based on antibodies within at least five t½ of that drug; hypogammaglobulinaemia (total p-IgG < 3 g/L); Treatment with rituximab or cyclophosphamide within six months before screening.

Treatments included imlifidase 0.25 mg/kg or 0.50 mg/kg, administered by intravenous infusion, as a single dose (no second dose). Timing: day of transplantation (patient with a

deceased donor) or day before transplantation (patients with a living donor). Planned 1.0 mg/kg and 2.0 mg/kg doses were in the protocol, but not used.

Non-investigational treatments included induction therapy given according to clinical practice at each site. If indicated, anti-thymocyte globulin derived from horse was given since rabbit anti-thymocyte globulin is cleaved by imlifidase. Premedication of methylprednisolone 250 mg intravenous and 10 mg oral loratadine before each imlifidase infusion. Prophylaxis of 1 g phenoxymethylpenicillin once per day, single dose of cefuroxime prior to transplantation, trimethoprim 80 mg/sulfamethoxazole 400 mg once per day, valganciclovir once per day for three months after transplantation. Immunosuppressants: Tacrolimus 0.1 mg/kg bodyweight twice per day, and mycophenolate Mofetil 500 to 1000 mg twice daily orally. Prednisolone (reducing dose over three months, then 5 mg once per day). Rejection episodes were managed using standard of care.

Baseline characteristics: 12 patients were screened with ten included (five each in the 0.25 mg/kg and 0.5 mg/kg groups). All the patients completed the study and were included in all the analysis datasets. Baseline patient demographics and disease characteristics are shown in Table 10.

Magnitude of the treatment effect and its clinical significance

Main efficacy endpoint included post-imlifidase, all ten patients had HLA antibody levels acceptable for transplantation and negative cross-match tests. In each treatment group (five patients each), four patients received a kidney from a deceased donor, and one received a live donor kidney.

Other efficacy endpoints include:

- Anti-HLA antibodies (analysed with SAB-HLA): both groups had a similar response, with a rapid decrease at 1 hour post infusion and recovery from Day 7.
- Anti-HLA antibodies (analysed with SAB-C1q), both groups also had a similar response, with a rapid decrease at 1 hour post infusion.
- Donor specific antigens: detected in eight patients, and decreased by one hour following imlifidase infusion and recovered from Day 7.
- Cytotoxic sera screen: become negative in 2 of 3 patients in the 0.25 mg/kg group and 1 of 3 in the 0.5 mg/kg group.
- Cross-matches using flow cytometry and CDC CXM for B-cells: none positive.
- Time to recovery of IgG (analysed in four patients; the six other patients did not have recovery of IgG to pre-transplant levels): In two patients in the 0.25 mg/kg group the time to recovery was 122 days and 160 days. In two patients in the 0.5 mg/kg group, time to recovery was 22 days and 63 days.
- The median (range) time to 80% recovery of SAB-HLA antibodies: 68 (29 to 181) days in the 0.25 mg/kg group and 15 (8 to 62) days in the 0.5 mg/kg group.
- IgG cleavage occurred in the first two hours after imlifidase infusion for both dose levels. Recovery occurred from Day 7. Intact IgG was rapidly converted to scIgG and then into F(ab')2 and Fc fragments within one hour.
- Kidney function: All were functional at the end of the study. At Day 180, serum creatinine was above the normal range, but within the expected range for renal transplant patients (< 200 µmol/L).
- Six month kidney biopsy results: normal for all in the 0.25 mg/kg group and for two patients in the 0.50 mg/kg group. The remaining three patients in the high dose group showed

chronic antibody-mediated rejection (AMR) for one patient and chronic donor-originated changes for two patients. All three patients with abnormal kidney biopsy findings on Day 180 had rejection reported as an adverse event (AE) during the study.

Study 02 (13-HMedIdeS-02)

Study 02 is an open label, single arm (no comparator), non-randomised, ascending dose, dose finding Phase II study to evaluate safety, tolerability, efficacy and PK of imlifidase in renal transplantation in eight adult men and women (aged 18 years or above) with ESRD and relevant antibodies. The study was conducted at two sites in Sweden from June 2014 to February 2015.

Primary objective is to find an imlifidase dosing scheme which in the majority of the patients resulted in HLA antibody levels which were acceptable for transplantation.

Main efficacy objective is to find an imlifidase dose which in the majority of the patients resulted in HLA antibody levels acceptable for transplantation, within 24 hours from dosing.

Other objectives included other efficacy, safety, PK, and PD objectives.

Inclusion criteria included age 18 years or above patient; CKD and in dialysis with identified antibodies against at least two HLA antigens of which at least one is MFI ≥ 3000 (SAB assay) on at least two occasions.

Treatments: Four dose groups were planned: 0.12, 0.25, 0.50 and 1.0 mg/kg, given once or twice over 15 min, within a maximum of two days and a total study time of 64 days. 1.0 mg/kg was not used. Eight patients were included and given imlifidase: three patients were given two doses of 0.12 mg/kg (0.24 mg/kg in total); two patients were given 0.25 mg/kg once; two patients were given two doses of 0.25 mg/kg (0.50 mg/kg in total). One patient was given 0.25 mg/kg, but the infusion was disrupted after about 4 minutes due to infusion reactions.

Non-investigational treatments were premedication: methylprednisolone 250 mg intravenous and, loratadine 10 mg orally; Prophylactic antibiotic treatment; Details of immunosuppressants were not provided.

Baseline patient demographics and disease characteristics are shown in Table 10.

Magnitude of the treatment effect and its clinical significance

The two patients treated with 0.50 kg/kg both achieved the efficacy outcome. The C1qScreen data indicated complete response for all the patients.

Using PRA, in the 0.24 mg/kg group at 24 hours post dose T-cell PRA was 0 to 7% and B-cell PRA was 0 to 21%. There was greater response in the 0.25 mg/kg and 0.50 mg/kg patients.

The patients initially treated with 0.12 mg/kg were all given a second dose. IgG concentrations decreased further following the second dose in all three patients. After the second dose, concentrations decreased to approximately 10 µg/mL. Following 25 mg/kg concentrations decreased to approximately 10 µg/mL and decreased further in the two patients who received a second 25 mg/kg dose.

Study 13 (17-HMedIdeS-13)

Study 13 was a retrospective follow-on study of the patients in Study 02 and Study 03. The study included those patients who had received a full dose of imlifidase and a kidney transplant. The study was conducted at two sites in Sweden from April 2018 to May 2018.

Primary objective is to collect additional data from donor and recipients who have been treated with imlifidase prior to kidney transplantation.

Data were collected from medical records, laboratory results, pathology reports and other source documents for the time period from time of imlifidase administration to 2 or 6 months after administration.

There were 11 patients (six males and five females): one from Study 02 (treated with 2 x 0.12 mg/kg; 0.24 mg/kg (total)); and 10 from Study 03 (five treated with 0.25 mg/kg and five treated with 0.5 mg/kg).

Baseline characteristics: Five patients had previous transplantations. Time on the waiting list ranged from 128 days to 8 years. HLA mismatch counts ranged from 5 to 14 HLA mismatches per patient. The historical peak PRA values ranged from 17% to 100%. Five of the patients had cPRA values ≥ 80% at an MRI cut-off level of 2,000.

Two of the donor kidneys were live donors, one related and the other unrelated. Nine of the donor kidneys were from deceased donors. Cold ischaemia time ranged from 6 hours to 21 hours and six were stored using cold machine perfusion.

Magnitude of the treatment effect and its clinical significance

Delayed graft function was not reported in Study 02 or Study 03, and none of the patients suffered a graft loss during the six month follow up period. 4 out of 11 (36%) experienced seven suspected rejection episodes (reported as AE/serious adverse event (SAE)) within four months of transplantation.

Biopsies were taken at six of the episodes and 3 out of 11 (27%) patients had biopsy-confirmed AMR with C4d depositions and presence of DSA, while two were classified as CMR and 1 as a mixed AMR/CMR (Table 11). All rejection episodes were treated and resolved within the study period.

Table 10: Study 13 Evaluation of reported rejection episodes.

Diagnosis	Day	Reason for biopsy	AE/SAE	DSA	eGFR (mL/min/1.73 m²) / (relative day)	C4d(X[a])	Sponsor judgement
Antibody-mediated rejection	11	Elevated creatinine levels	SAE	5 DSA, high level	15 / (Day 15)	C4d(3)	Active AMR
Kidney borderline rejection	82	Elevated creatinine levels	SAE	5 DSA, high level	60 / (Day 90)	C4d(3)	Active AMR and borderline CMR
Kidney borderline rejection	26	Elevated creatinine levels	SAE	1 DSA high-level	30 / (Day 28)	C4d(3)	Active AMR
Rejection	14	Elevated creatinine levels	SAE	1 DSA high level	39 / (Day 19)	C4d(3)	Active AMR and CMR
Rejection	61	Elevated creatinine levels	SAE	-	16 / (Day 64)	NEG	Biopsy-proven CMR
Rejection	106	Elevated creatinine levels	AE	-	39 / (Day 120)	NEG	Biopsy-proven CMR

[a] Grade of C4d staining

Study 14 (17-HMedIdeS-14)

Study 14 is an ongoing five-year, observational follow up study of the patients in feeder Studies 02, 03, 04 and 06. Up to 46 patients could be included. Four follow up visits at 1, 2, 3 and 5 years after imlifidase administration were planned.

Primary objective is to evaluate graft survival in subjects who have undergone kidney transplantation after imlifidase administration.

34 out of 46 patients transplanted in the feeder (Phase 2) studies have been actively enrolled. Three of the 34 patients had experienced graft loss after end of the feeder studies, but prior to enrolment in the long-term follow-up study. Data from a further three patients (who died after the feeder studies, but prior to enrolment for the Study 14) were presented with relevant ethics approval. From study start 37 patients were providing data in the full-analysis set (FAS). Some patient data are completely or partially missing, introducing multiple sources of bias.

Magnitude of the treatment effect and its clinical significance

This follow-up study is ongoing with final results expected in fourth quarter of 2023. Only preliminary results are available.

Primary endpoint (at 1, 2, 3 and 5 years after first dose of imlifidase): Overall graft survival (defined as time from transplantation to graft loss; graft loss was defined as permanent return to dialysis for at least 6 weeks, re-transplantation, or transplantectomy).

Overall graft survival at the 3-year assessment was 85% (based on the population in Study 14) (Table 12). 2 out of the 3 graft losses were due to lowering or non-compliance of immunosuppression medication with the third being a decline in graft function over time.

Table 11: Study 14 Primary endpoint: death-censored graft survival by time period

	6 months N=46[2]	6 months-1 year N=36	1-2 years N=33	2-3 years N=33	3-5 years N=17
Graft survival	n (%)	n (%)	n (%)	n (%)	n (%)
Yes	43 (93)	36 (100)	33 (100)	30 (91)	17 (100)
No	3 (7)	0	0	3 (9)	0

Source: EOT-Table 14.1.5, EOT-Table 14.1.6, EOT-Listing 16.2.6.3
N=number of patients in full analysis set; n=number of patients with data
Graft survival is assumed at earlier timepoints if 'Yes' at a later time-point
[1]One patient in FAS was lost to follow up, i.e. does not contribute to the graft survival information
[2]Data from all patients potentially eligible to participate in Study 14 at the end of the feeder studies

Selected secondary endpoints (at 1, 2, 3 and 5 years after the first dose of imlifidase) included:

- Kidney function: shown in Table 13.
- Donor specific antibody rebound (defined as any re-occurrence of a DSA with an MFI value ≥ 2000 at any time): shown in Table 14.

Table 12: Study 14. Kidney function by means of eGFR by year

	6 months n=33	1 year n=27	2 years n=28	3 years n=29	5 years n=17
eGFR category	n (%)	n (%)	n (%)	n (%)	n (%)
<30 mL/min/1.73 m^2	4 (12)	1 (4)	1 (4)	3 (10)	3 (18)
30-59 mL/min/1.73 m^2	18 (55)	16 (59)	17 (61)	15 (52)	7 (41)
60-90 mL/min/1.73 m^2	11 (33)	10 (37)	10 (36)	11 (38)	7 (41)

Source: EOT-Table 14.1.13
N=number of patients in full analysis set; n=number of patients with data
Some patients have data for later but not for earlier time points since they were included in the study after their initial visits should have taken place. As described in Amendment 02, Section 5.8.1 data on kidney function has been permitted to be retrieved from the patient's medical records for these patients. Collected data only are included in the table, no imputations have been made.
The one (1) patient in the FAS who is considered lost to follow up signed informed consent but did not attend any visits, however a creatinine value from the 1-year assessment was collected retrospectively for this patient.

Table 13: Study 14. Occurrence of any DSA with MFI ≥ 2000 by year

	6 months n=28	1 year n=6	2 years n=13	3 years n=23	5 years n=10
DSA MFI value	n (%)	n (%)	n (%)	n (%)	n (%)
<2000	11 (39)	4 (67)	7 (54)	17 (74)	6 (60)
≥2000	17 (61)	2 (33)	6 (46)	6 (26)	4 (40)

Source: EOT-Listing 16.2.6.12
N=number of patients in full analysis set; n=number of patients with data.
Not all patients have had all visits. Only actual data are included, no imputations are made.
[1]One patient in FAS was lost to follow up, i.e. does not contribute to the data

Planned or ongoing studies without available results

The following studies are planned or ongoing without available results (Table 15) protocols are available for Studies 17 and 19.

- Study 17 (20-HMedIdeS-17) (Figure 3 and Figure 4): an open-label, controlled (to standard of care), randomised (1:1), multi-centre Phase III trial with 64 adult patients (aged 18 to 70 years) with CKD Stage 5, highly sensitised (cPRA ≥ 99.9%) and with a positive crossmatch against an available deceased donor kidney. The trial period from screening is 12 to 15 months for all patients (results expected second quarter of 2025).
  - Primary endpoint: Mean eGFR at 12 months.

Table 14: Ongoing studies of Idefirix

Study and status	Summary of Objectives	Confirmatory nature	Key milestones	Recruitment status	Proposed submission date- clinical study report
Clinical Trial Study ID 17-HMedIdeS-14 Status: Fully enrolled and ongoing	To confirm the long-term efficacy of imlifidase in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor.	To provide descriptive evidence of long-term safety and efficacy. Observational long-term follow-up study from patients recruited from the 6-month endpoint phase 2 studies where imlifidase facilitated transplantation.	Protocol finalised = 03 April 2018 First patient first visit= 03 July 2018 Last patient last visit = 15 February 2023 (postponed into this date due to patient having covid)	N = 37 patients Fully recruited	Q4 2023
Clinical Trial Study ID 20-HMedIdeS-19 Status: Ongoing	A controlled, open-label post-authorisation efficacy and safety study in imlifidase desensitised kidney transplant patients with positive crossmatch against a deceased donor prior to imlifidase treatment, including non-comparative registry and concurrent reference cohorts. EU based	1-year graft survival, 1 year kidney function, and safety in kidney transplanted patients with donor specific antibodies, who have been treated with imlifidase.	Protocol finalised =18 October 2021 First patient first visit= Q2 2022 Last patient last visit = Planned Q4 2024	N = 50 patients in the imlifidase treated cohort Recruitment has started in May 2022	Q4 2025

Study and status	Summary of Objectives	Confirmatory nature	Key milestones	Recruitment status	Proposed submission date- clinical study report
Clinical Trial Study ID 20-HMedIdeS-17 Status: Ongoing	A USA exclusive open-label, controlled, randomized Phase 3 trial evaluating 12-month kidney function in highly sensitised (cPRA ≥99.9%) kidney transplant patients with positive crossmatch against a deceased donor, comparing desensitisation using imlifidase with standard of care	Confirmatory efficacy and safety	Protocol finalised = 30 Nov 2021 First patient first visit= 21 December 2021	Enrolling N = 64 patients Enrolled as of 21 February 2023 = 59	

Figure 3: Study 17 Trial design (prior to randomisation)

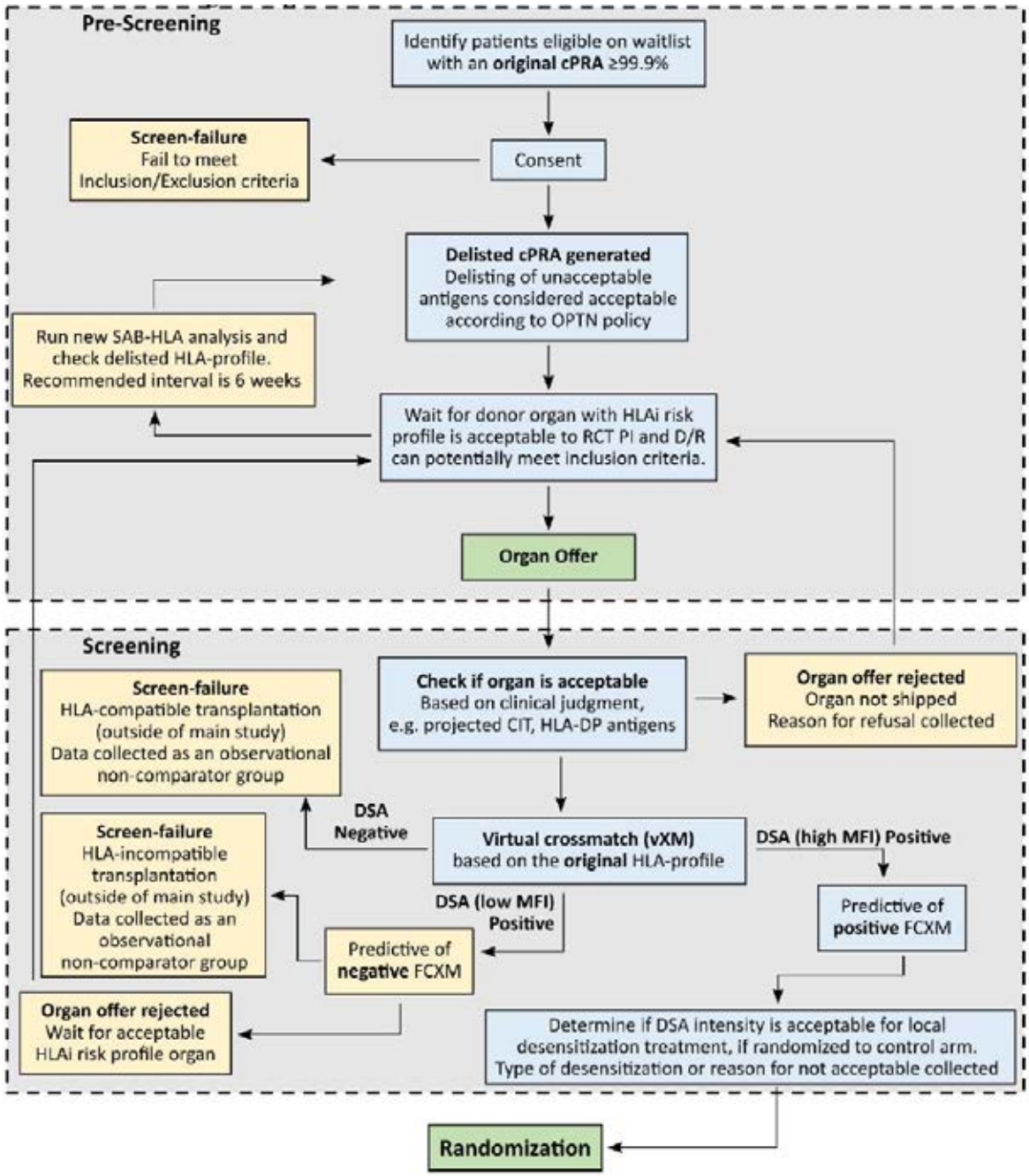
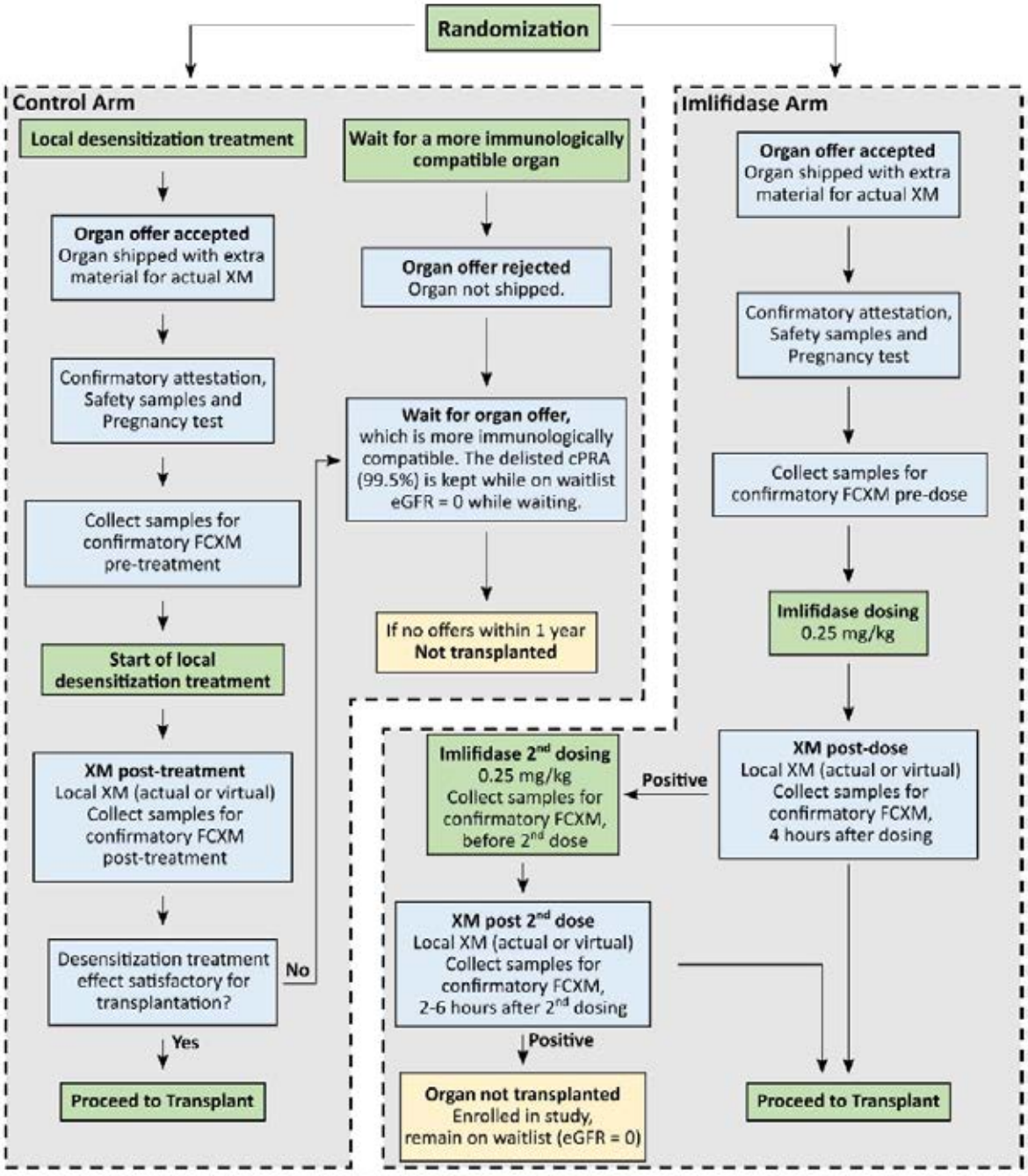


Figure 4: Study 17 Trial design (after randomisation)



CIT=Cold ischemia time; cPRA=Calculated panel reactive antibodies; D/R=Donor/Recipient; DSA=Donor specific antibodies; eGFR=Estimated glomerular filtration rate; FCXM=Flow cytometry crossmatch; HLA=Human leukocyte antigen; HLAi=Human leukocyte antigen incompatible; MFI=Mean fluorescence intensity; OPTN=Organ Procurement and Transplantation Network; RCT PI=Randomized controlled trial Principal investigator; SAB-HLA=Single antigen bead - Human leukocyte antigen; vXM=Virtual crossmatch; XM=Crossmatch

- Study 19 (20-HMedIdeS-19): a controlled, open label, post-authorisation, Phase III efficacy and safety trial in imlifidase desensitised kidney transplant patients (aged 18 to 75 years) with positive crossmatch against a deceased donor prior to imlifidase treatment, including non-comparative registry and concurrent reference cohorts at multiple sites in European Union and United Kingdom (results expected fourth quarter of 2025).
  - Primary endpoint: 1-year graft failure-free survival in patients who have been kidney transplanted after imlifidase treatment.

- Study 20 (20-HMedIdeS-20): a prospective, post-authorisation long-term follow up trial including a noncomparative concurrent reference cohort (5-year follow-on from Study 19) (results expected fourth quarter of 2030).
- Study 25 (21-HMedIdeS-25): a prospective, long-term, confirmatory follow up trial (3-year follow-on from Study 17).

Safety

Exposure

As of February 2022, 139 patients and volunteers have received imlifidase in clinical trials.

In the clinical trials provided in the dossier (Table 16) 53 patients have been treated with imlifidase and 46 were transplanted. 43 were treated with 0.24 or 0.25 mg/kg and 10 with 0.5 mg/kg. 46 patients were followed up for 6 months, 39 for 12 months, 24 for 24 months, 11 for 36 months and one for 60 months (Table 17).

Table 15: Phase II studies (CKD population). Exposure and follow-up by total dose (safety set)

		0.25 mg/kg (N=43)	0.50 mg/kg (N=10)	Total (N=53)
No. of infusions	n	43	10	53
	1; n (%)	(1x0.24/0.25 mg/kg): 40 (93%)	(1x0.50 mg/kg): 5 (50%)	45 (85%)
	2; n (%)	(2x0.12 mg/kg): 3 (7%)	(2x0.25 mg/kg): 5 (50%)	8 (15%)
Time between the first and the last treatment (h)	n	3	5	8
	Mean (SD)	28.84 (0.64)	19.93 (9.87)	23.27 (8.78)
	Median	28.87	13.47	28.53
	Min; Max	28.2; 29.5	11.6; 30.8	11.6; 30.8
Cumulative duration of follow-up after treatment (months) - until end of study date	1; n (%)	42 (98%)	10 (100%)	52 (98%)
	2; n (%)	42 (98%)	9 (90%)	51 (96%)
	3; n (%)	36 (84%)	8 (80%)	44 (83%)
	6[a]; n (%)	20 (47%)	5 (50%)	25 (47%)
	6 (±14 days); n (%)	31 (72%)	8 (80%)	39 (74%)
Subject follow-up - until end of study	Subject years			22.9

[a] 6 months is defined as at least 180 days. The category '6 months (±14 days)' includes subjects with at least 166 days between the last treatment date and end of study date; SD: standard deviation

Table 16: Long-term follow-up of transplanted patients at 6, 12, 24, 36 and 60 months by total dose (safety set; transplanted)

	Months	0.25 mg/kg (N=38) n (%)	0.50 mg/kg (N=8) n (%)	Total (N=46) n (%)
Cumulative duration of follow-up after treatment (months) - until the last contact	6	38 (100%)	8 (100%)	46 (100%)
	12	33 (87%)	6 (75%)	39 (85%)
	24	19 (50%)	5 (63%)	24 (52%)
	36	10 (26%)	1 (13%)	11 (24%)
	60	1 (3%)		1 (2%)

Note: 6 months: ≥ 180 days; 12 months: ≥ 365 days; 24 months: ≥ 730 days; 36 months: ≥ 1095 days; 60 months: ≥ 1825 days

Adverse event overview

Phase I studies (healthy males): 10 out of 14 subjects (71%) receiving placebo reported at least one treatment emergent adverse event (TEAE) . The percentage with at least one TEAE was similar among those receiving imlifidase of Process 1 in Study 01 (18 out of 20 subjects [90%]) and those receiving imlifidase of Process 2 in Study 15 (13 out of 15 subjects [87%]), noting small subject numbers.

Phase II studies (CKD population): All 53 patients had at least one treatment emergent adverse event (TEAE) – i.e., AE defined as occurring within 30 days of imlifidase administration, with a total of 468 TEAEs. The three most commonly reported TEAEs were hyperkalaemia (17 [32%]), anaemia (17 [32%]), and constipation (16 patients [30%]) (Table 18). There was no obvious difference between the dose groups, noting the low patient number in the 0.50 mg/kg group (n = 10) that precludes definite conclusions. Furthermore, there were differences with regard to AESI (see below; 40% versus 80%).

Table 17: Phase II studies (CKD population) treatment emergent adverse events by Preferred Term occurring in at least 5% of patients (safety set) by transplantation status

	Number of Subjects (% of Subjects) and Number of Events		
	Transplanted (N=46)	Not Transplanted (N=7)	Total (N=53)
Subjects	46 (100.0) 434	7 (100.0) 34	53 (100.0) 468
Hyperkalaemia	17 (37.0) 18		17 (32.1) 18
Anaemia	15 (32.6) 15	2 (28.6) 2	17 (32.1) 17
Constipation	16 (34.8) 20		16 (30.2) 20
Nausea	12 (26.1) 15	1 (14.3) 1	13 (24.5) 16
Transplant rejection	12 (26.1) 14		12 (22.6) 14
Hypomagnesaemia	9 (19.6) 11		9 (17.0) 11
Vomiting	9 (19.6) 11		9 (17.0) 11
Diarrhoea	9 (19.6) 9		9 (17.0) 9
Dyspepsia	8 (17.4) 9		8 (15.1) 9
Pruritus	7 (15.2) 7	1 (14.3) 1	8 (15.1) 8
Complications of transplant surgery	7 (15.2) 8		7 (13.2) 8
Fluid overload	7 (15.2) 7		7 (13.2) 7
Headache	5 (10.9) 5	1 (14.3) 2	6 (11.3) 7
Delayed graft function	6 (13.0) 6		6 (11.3) 6
Hyperglycaemia	5 (10.9) 5	1 (14.3) 1	6 (11.3) 6
Hypotension	6 (13.0) 6		6 (11.3) 6
Urinary tract infection	6 (13.0) 6		6 (11.3) 6
Dyspnoea	5 (10.9) 6		5 (9.4) 6
Hypocalcaemia	5 (10.9) 6		5 (9.4) 6
Hypertension	5 (10.9) 5		5 (9.4) 5
Pyrexia	5 (10.9) 5		5 (9.4) 5
Oedema peripheral	4 (8.7) 6		4 (7.5) 6
Flatulence	4 (8.7) 5		4 (7.5) 5
Alanine aminotransferase increased	3 (6.5) 3	1 (14.3) 1	4 (7.5) 4
Anxiety	4 (8.7) 4		4 (7.5) 4
Blood creatinine increased	4 (8.7) 4		4 (7.5) 4
Donor specific antibody present	4 (8.7) 4		4 (7.5) 4
Hyperphosphataemia	4 (8.7) 4		4 (7.5) 4
Hypertriglyceridaemia	4 (8.7) 4		4 (7.5) 4
Hypophosphataemia	4 (8.7) 4		4 (7.5) 4
Pain	4 (8.7) 4		4 (7.5) 4
Tremor	3 (6.5) 3	1 (14.3) 1	4 (7.5) 4
Urine output decreased	4 (8.7) 4		4 (7.5) 4
Aspartate aminotransferase increased	2 (4.3) 2	1 (14.3) 2	3 (5.7) 4
Infusion related reaction	2 (4.3) 3	1 (14.3) 1	3 (5.7) 4
Abdominal distension	3 (6.5) 3		3 (5.7) 3
Drug hypersensitivity	3 (6.5) 3		3 (5.7) 3
Fatigue	2 (4.3) 2	1 (14.3) 1	3 (5.7) 3
Hypokalaemia	3 (6.5) 3		3 (5.7) 3
Hyponatraemia	2 (4.3) 2	1 (14.3) 1	3 (5.7) 3
Incision site complication	3 (6.5) 3		3 (5.7) 3
Insomnia	3 (6.5) 3		3 (5.7) 3
Metabolic acidosis	3 (6.5) 3		3 (5.7) 3
Muscle spasms	3 (6.5) 3		3 (5.7) 3
Procedural pain	3 (6.5) 3		3 (5.7) 3
Sepsis	3 (6.5) 3		3 (5.7) 3
Swelling	3 (6.5) 3		3 (5.7) 3

Treatment related adverse event (adverse drug reaction) overview

Adverse drug reaction overview

In the section below, treatment-emergent AEs and post-treatment emergent AEs assessed as related to imlifidase are presented, i.e., ADRs:

Phase II studies (CKD population): 18 out of 53 patients (34%) had at least one related TEAE. 4/53 patients (8%) had one related post-TEAEs each (Table 19).

Table 18: Phase II studies (CKD population) related treatment emergent adverse event and related post-treatment emergent adverse event by Preferred Term (safety set)

	No. of subjects (% of subjects) and No. of events		
	TEAE (N=53)	Post-TEAE (N=53)	Total (N=53)
Total	18 (34%) 37	4 (7.5) 4	19 (35.8) 41
Pneumonia	1 (2%) 1	2 (3.8) 2	3 (6%) 3
Urinary tract infection	3 (6%) 3		3 (6%) 3
Aspartate aminotransferase increased	2 (4%) 3		2 (4%) 3
Headache	2 (4%) 3		2 (4%) 3
Alanine aminotransferase increased	2 (4%) 2		2 (4%) 2
Infusion related reaction	2 (4%) 2		2 (4%) 2
Infusion site pain	2 (4%) 2		2 (4%) 2
Myalgia	2 (4%) 2		2 (4%) 2
Sepsis	2 (4%) 2		2 (4%) 2
Dizziness postural	1 (2%) 2		1 (2%) 2
Abdominal infection		1 (2%) 1	1 (2%) 1
Adenovirus infection	1 (2%) 1		1 (2%) 1
Anaemia	1 (2%) 1		1 (2%) 1
Blood phosphorus increased	1 (2%) 1		1 (2%) 1
Blood triglycerides increased	1 (2%) 1		1 (2%) 1
Catheter site infection	1 (2%) 1		1 (2%) 1
Escherichia test positive	1 (2%) 1		1 (2%) 1
Flushing	1 (2%) 1		1 (2%) 1
Hypotension	1 (2%) 1		1 (2%) 1
Infection	1 (2%) 1		1 (2%) 1
Influenza	1 (2%) 1		1 (2%) 1
Parvovirus infection		1 (2%) 1	1 (2%) 1
Postoperative wound infection	1 (2%) 1		1 (2%) 1
Rash	1 (2%) 1		1 (2%) 1
Transplant rejection	1 (2%) 1		1 (2%) 1
Upper respiratory tract infection	1 (2%) 1		1 (2%) 1
Wound infection	1 (2%) 1		1 (2%) 1

Each subject could have both TEAEs and post-TEAEs and may therefore be presented in both columns.

Deaths

No deaths occurred in the core clinical studies with imlifidase or in completed or ongoing studies with imlifidase in other indications.

Serious adverse events

Phase I studies (healthy males): No SAEs.

Phase II studies (CKD population): 112 SAEs were reported by 38 out of 53 patients (72%). 20 out of 53 patients (38%) had a TESAE of severe intensity. 11 out of 53 patients (21%) had 12 related SAEs (52.3 related SAEs per 100 subject-follow-up-years). Related SAEs included: pneumonia (three patients [6%]), sepsis (two patients [4%]), and abdominal infection, catheter site infection, parvovirus infection, upper respiratory tract infection, infusion-related reaction, myalgia, and transplant rejection (1 patient [2%]) each). 42% of the SAEs started ≤ 30 days of the last dose and 58% started > 30 days. The duration was ≤ 30 days for 82% of the SAEs.

Adverse events of special interest

The following potential adverse events of special interests (AESI) were pre-defined: severe or serious infections (for example, potentially due to the temporarily lowered IgG levels) (Table 20); infusion-related reactions; serum sickness; myalgia.

Table 19: Phase I and II studies (healthy volunteers (HV) and CKD population) Related Potential AESIs of Severe or serious infections.

		No. of subjects (% of Subjects) and No. of events			
	Transplanted (N=47)	Not transplanted (N=7)	HV imlifidase (Study 01) Process 1 (N=20)	HV imlifidase (Study 15) Process 2 (N=15)	HV placebo (N=14)
Total	**7 (15%) 9**	**2 (29%) 2**	**0**	**0**	**0**
Abdominal infection	1 (2%) 1	0			
Catheter site infection	1 (2%) 1	0			
Infection	1 (2%) 1	0			
Parvovirus infection	1 (2%) 1	0			
Pneumonia	2 (4%) 2	1 (14%) 1			
Sepsis	2 (4%) 2	0			
Upper respiratory tract infection	0	1 (14%) 1			
Urinary tract infection	1 (2%) 1	0			

Related potential AESIs within the AESI 'Severe or serious infections' by PT and subpopulation (all treated).

25 out of 53 patients (47%) experienced 41 potential AESIs (Table 21): 17 out of 43 (40%) receiving a total imlifidase dose of 0.25 mg/kg and 8 out of 10 (80%) receiving a total dose of 0.50 mg/kg.

Table 20: Phase II studies (CKD population) adverse events of special interest by total dose (safety set).

	No. of subjects (% of subjects) and No. of events		
	0.25 mg/kg (N=43)	0.50 mg/kg (N=10)	Total (N=53)
Total	**17 (40%) 30**	**8 (80%) 11**	**25 (47%) 41**
Infusion-related reactions	3 (7%) 3	0	3 (6%) 3
Serum sickness [a]	0	0	0
Severe or serious infections	15 (35%) 27	7 (70%) 10	22 (42%) 37
Severe or serious myalgia	0	1 (10%) 1	1 (2%) 1

[a] Serum sickness occurred in Study 08 evaluating imlifidase in patients with TTP (serum sickness did not occur in patients with ESRD)

All AESIs of 'Infusion-related reaction' occurred in the 0.25 mg/kg group (three patients [7%]). 'Severe or serious infections' were imbalanced (35% versus 70%). 'Severe or serious myalgia' only occurred in the higher (0.5 mg/kg) dose group. The patient numbers are too small for definite conclusions, in particular in the absence of an inactive comparator group.

Long term safety in ongoing Study 14 (follow-up of patients from Studies 02, 03, 04 and 06. Study 14)

Additional to three events of graft loss in the core studies, another three events of graft loss occurred after the core studies: one case of a transplant with poor function followed by a rejection episode and gradual decline of function; one case due to non-compliance with immunosuppression therapy; and one case occurring after reduction of immunosuppression therapy due to infection. No related SAE has been reported at the data lock point (DLP). Three deaths occurred and none were considered related to imlifidase.

Immunogenicity and anti-drug antibody

Antibodies against imlifidase are not uncommon due to previous exposure to *S. pyogenes*. No IgE antibodies were detected in any patient in the clinical studies. The sponsor postulated that infusion reactions likely resulted from mechanisms not specific to imlifidase.

At Baseline, at least 85% of patients had detectable anti-imlifidase IgG. These antibodies were cleaved along with the rest of the IgG and were rarely detectable after 2 to 6 hours post dose. The anti-imlifidase IgG recovered after seven days and peaked several weeks after treatment at higher than baseline concentrations.

However, the anti-imlifidase antibodies did not appear to interfere with treatment or cause adverse effects. Population PK/PD modelling did not suggest a clinically significant effect between pre-dose ADA levels and the PD effect of imlifidase at the proposed dose.

Post-market reports

Three periodic safety update reports (PSUR) were provided for the following time periods:

- 25 August 2020 to 25 February 2021: during this time period there were no SAEs from individual named patient use programs or from ongoing clinical trials.
- 26 February 2021 to 25 August 2021: during the reporting interval there was one serious infection with *E. coli*.
- 26 August 2021 to 25 February 2022: as of February 2022: Five patients were exposed who were not in clinical trials. There were three reports of off-label use for other medical conditions. There was one serious adverse reaction reported from a clinical trial: acute kidney injury. Cumulatively, 11 patients have received imlifidase through individual named patient use programs. Cumulatively, six non-serious ADRs were received from spontaneous post-marketing sources.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 1.0 (dated 16 June 2020; data lock point (DLP) 1 December 2019) and Australia specific annex (ASA) version 0.1 (dated 14 June 2022) in support of this application. In response to TGA's questions, the sponsor has submitted updated ASA version 0.2 (dated 21 February 2023) in support of its application. The related EU-RMP is still version 1.0.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 22. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 21: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Severe or serious infection	ü	ü	ü	–
	Infusion-related reactions	ü	ü	ü	–
Important potential risks	None	–	–	–	–
Missing information	None	–	–	–	–

Pharmacovigilance plan

Only routine pharmacovigilance activities are proposed in the EU-RMP and the ASA. However, there is a clinical study plan for Provisional Registration in the ASA (termed post-authorisation efficacy studies in the EU-RMP). (Table 23)

Table 22: Ongoing and planned studies

Safety Concern	Additional activity	Proposed actions/outcomes	Planned submission
Ongoing studies			
Severe or serious infection	Study 14 (17-HMedIdeS-14)	An ongoing observational long-term follow-up study to evaluate long-term graft survival and clinical outcome after imlifidase.	Fourth quarter of 2023
Severe or serious infection Infusion-related reactions	Study 19 (20-HMedIdeS-19)	A post-authorisation efficacy study (PAES) to evaluate 1-year graft survival, kidney function and safety after imlifidase (including infusion related reactions).	Fourth quarter of 2025
	Study 17 (20-HMedIdeS-17)	A USA exclusive open-label, controlled, randomised Phase III trial evaluating 12-month kidney function in highly sensitised (cPRA ≥99.9%) kidney transplant patients with positive crossmatch against a deceased donor, comparing desensitisation using imlifidase with standard of care.	
Planned Studies			
Severe or serious infection	Study 20 (20-HMedIdeS-20)	A 5-year-extension to the post-authorisation efficacy study 19 (20-HMedIdeS-19) to evaluate long-term graft survival in patients who have undergone kidney transplantation after imlifidase administration.	Fourth quarter of 2030
	Study 25 (21-HMedIdeS-25)	A 3-year-extension to the USA Phase III efficacy study 17 (20-HMedIdeS-17) to evaluate long-term graft survival in patients who have undergone kidney transplantation after imlifidase administration.	

Risk minimisation plan

Recommended wording for conditions of registration

The suggested wording is:

'*The Idefirix EU-Risk Management Plan (RMP) (version 1.0, dated 16 June 2020, data lock point 1 December 2019), with Australia Specific Annex (version 0.2, dated 21 February 2023), included with submission PM-2022-02499-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*'

The following wording is recommended for the PSUR requirement:

'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.'

The following wording is recommended for the Black Triangle Scheme condition of registration:

'Idefirix (imlifidase) is to be included in the Black Triangle Scheme. The PI and CMI for Idefirix must include the black triangle symbol and mandatory accompanying text for five years, or the product's entire period of provisional registration, whichever is longer.'

As Idefirix is being considered for a provisional registration, confirmatory trial data is recommended for the condition of registration. The following wording based on the proposed clinical study plan is provided as a preliminary suggestion for the TGA Delegate to consider. The final condition of registration is to be determined by the TGA Delegate:

'*Specifically, the sponsor must conduct studies as described in the clinical study plan in version 0.2 (dated 21 February 2023) of the Australia Specific Annex. The following study report(s) should be submitted to TGA:*

- *Study 17-HMedIdeS-14, by Q4 2023*
- *Study 20-HMedIdeS-19 by Q4 2025*
- *Study 20-HMedIdeS-17*

Further guidance for sponsors is available on the TGA website.'

Risk-benefit analysis

Delegate's considerations

Pharmacology

The pharmacokinetic and pharmacodynamic profiles of imlifidase has been adequately characterised for the proposed usage, that is restricted to a single intravenous dose, with a facultative second intravenous dose. This pharmacodynamic profile has been explored at different dose levels and the time-course effect has been described.

Efficacy

Clinical trial program overview

No Phase III comparative studies: There were no completed Phase III studies and thus Phase III confirmatory data have not been presented. No comparative studies have been conducted to test efficacy.

Hypothesis testing: The Phase I and II studies presented by the sponsor were not designed as definitive tests of efficacy. The studies did not perform any hypothesis tests for efficacy and the outcome measures were not designed in a way that would enable such testing. There are clearly some barriers to the performing of hypothesis tests for efficacy for imlifidase. There are potential ethical issues in control group design when the consequences of treatment failure are severe.

Inclusion and exclusion criteria (Table 24): In the Phase II studies, the main inclusion criteria were age at least 18 years; a CKD diagnosis and waiting list for kidney transplantation; sensitised with anti-HLA antibodies. In Studies 04 and Study 06, a positive cross-match was required (not required in Studies 02 or 03; positive T-cell CDCXM was an exclusion criterion in Study 03). Only Study 04 had a previous desensitisation attempt with rituximab and IVIg as an inclusion criterion. Study 04 also excluded living donors.

Bias: There were a number of sources of bias and confounding. The sample size was rather small. All studies were non-randomised without a comparator group, and all open-label. For the follow-up Study 14, a few patients were lost to follow-up, potentially leading to attrition bias and/or survivor bias.

Table 23: Phase II studies. Overview of inclusion criteria

Inclusion criterion	Study 02	Study 03	Study 04	Study 06 Sweden, US	Study 06 France
≥18 years of age	X	X	X	X	X
CKD stage 5	X	X	X	X	X
Active on kidney transplantation waiting-list	X	X	X	X	X
Anti-HLA antibodies	≥1; MFI ≥3000	≥1; MFI >3000	cPRA ≥50%	PRA ≥80%[a]	≥1; MFI≥3000
Positive crossmatch			X	X	X
Previous desensitization			X		

[a]Sweden only

Clinical trial program results

The efficacy data can be summarised as:

- Study 06: 16 (88.9%) of the 18 transplanted patients had a functional kidney at end of study, with acceptable eGFR and off dialysis, including all five from living donors.
- Study 04: 16 (94%) of the 17 renal grafts functioning at the end of the study. Living donors were excluded from this study.
- Study 02 and Study 03: 11 (100%) patients with successful renal transplants, including two from living donors.

Study 14 (based on follow-up data of patients in Studies 02, 03, 04 and 06) and its primary objective to evaluate graft survival could be regarded as a key piece of the efficacy evaluation. Overall graft survival (Table 25):

- at the 6-month assessment was 43 out of 46 (93%); and
- at the 3-year assessment was 85%.

Two out of the three graft losses at three years were due to lowering or non-compliance of immunosuppression medication with the third being a decline in graft function over time.

Table 24: Study 14 Primary endpoint: death-censored graft survival by time period

	6 months N=46[2]	6 months-1 year N=36	1-2 years N=33	2-3 years N=33	3-5 years N=17
Graft survival	n (%)	n (%)	n (%)	n (%)	n (%)
Yes	43 (93)	36 (100)	33 (100)	30 (91)	17 (100)
No	3 (7)	0	0	3 (9)	0

Source: EOT-Table 14.1.5, EOT-Table 14.1.6, EOT-Listing 16.2.6.3
N=number of patients in full analysis set; n=number of patients with data
Graft survival is assumed at earlier timepoints if 'Yes' at a later time-point
[1]One patient in FAS was lost to follow up, i.e. does not contribute to the graft survival information
[2]Data from all patients potentially eligible to participate in Study 14 at the end of the feeder studies

Summary of the clinical trial program results:

The total of six graft losses (three by six months, and three by three years) are further analysed in Table 26. There were three HUT and three non-HUT patients. All were FCXM B-cell positive at Baseline, and 2 out of 6 were FCXM T-cell positive, noting that FCXM is regarded as much more sensitive compared to CDCXM.

Patients with a positive T-cell crossmatch typically have higher levels of sensitisation, and a risk of AMR and graft loss. This population was excluded in Study 03 but were able to participate in the other Phase II studies. There are only limited data on efficacy outcome with patients with a positive T-cell crossmatch.

At this stage, it does not appear that HUT or T-cell positive CXM patients are disproportionally more likely to suffer from graft failure after imlifidase administration, noting that no definite conclusions can be made due to small numbers.

Table 25: Phase II studies Characteristics of patients suffering graft loss

Population	HUT	HUT	HUT	Non-HUT	Non-HUT	Non-HUT
Sex	Male	Female	Male	Male	Male	Male
Age (years)	40	55	24	53	20	24
Donor	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased
cPRA (MFI cut-off 3000) (%)	100.00	96.95	100.00	94.50	86.07	93.09
FCXM T-cell	Negative	Positive	Positive	Negative	Negative	Negative
FCXM B-cell	Positive	Positive	Positive	Positive	Positive	Positive
Cold ischemia time (hours)	20.9	15.9	22.9	18.3	9.2	24.4
KDPI (%)	34	56	23	73	5	65
Time of graft loss	4 mon	37 mon	46 mon	Day 1	2 mon	36 mon

Dosing and treatment regimen

The development program has determined an appropriate dose and treatment regimen, and also used appropriate concomitant treatments including additional immunosuppression, antihistamines and prophylaxis against infection. This is reflected in the proposed PI.

Generalisability and applicability to the local patient population

The results of these trials performed in Sweden, France and the US can be reasonably extrapolated to Australia. Although there were some variations between the countries in the inclusion criteria, the study procedures were similar and can be applied to clinical practice in Australia. Living donor transplants were performed in Sweden, France and the US.

Living versus deceased donors

No jurisdiction has registered imlifidase for transplants from living donors.

The clinical trial program mainly used deceased donors. Of 46 patients treated with imlifidase prior to transplantation, 39 (85%) patients received deceased donor kidneys and 7 (15%) received living donor kidneys. All living donor transplants were successful, but the sample size is small.

For transplants from deceased patients, timely desensitisation is necessary and this may be not or less effectively achieved used currently available treatments.

Generally, transplants from living donor are more likely to succeed, and there is no inherent reason why imlifidase would not also be efficacious in living donor transplantation and could be restricted to scenarios in which other desensitisation treatments have failed or are contraindicated.

However, as stated above, the living donor sample size was much smaller compared to the deceased donor transplantation. Furthermore, the benefit-risk balance is different, as there are other more established desensitisation options available for transplantation from living donors, and typically there is more time to consider and use those. The main reason that prevents provisional registration of imlifidase for transplants from living donors is that they were specifically excluded from the confirmatory Phase III trials (Study 17 and Study 19).

Based on this, changes should be made to restrict the indication to transplants from deceased donors.

Planned/ongoing Phase III studies

The sponsor is planning or currently conducting relevant additional studies as outlined in Table 23. These studies are necessary to provide more efficacy and safety data for imlifidase. It is noted that none of the trials will include living donors.

Safety

The overall pattern of adverse effects is typical of patients undergoing renal transplantation.

The most commonly reported TEAEs were: hyperkalaemia in 17 (32.1%) patients, anaemia in 17 (32.1%), constipation in 16 (30.2%), nausea in 13 (24.5%), transplant rejection in 12 (22.6%), hypomagnesaemia in nine (17.0%), vomiting in nine (17.0%) and diarrhoea in nine (17.0%).

The treatment-related TEAEs were predominantly infectious disease AEs. The rate of treatment-related TEAEs was higher in the 0.5 mg/kg dose group: six (60.0%) patients compared with 13 (30.2%) patients treated with 0.24/0.25 mg/kg. However, in the absence of a control or reference group, it is difficult to attribute the events to imlifidase when the patients were also treated with high dose corticosteroids and immunosuppressive drugs.

There were no deaths during the clinical trials, but three deaths were recorded after completing the trials, but considered unlikely to be related to imlifidase.

The laboratory test abnormalities (for example, neutrophil increases) can be attributed to the underlying condition and high dose steroids. Changes in serum biochemistry were more likely attributable to transplantation rather than study treatment.

Adverse event of special interest

There was a high rate of infusion reactions, which, in the Phase II studies, did not have serious consequences. Infusion reactions occurred in three (5.6%) patients. There were two patients who ceased treatment due to infusion reactions, and another two who had their infusion interrupted because of mild infusion reactions.

Immunogenicity assessment

Antibodies against imlifidase are not uncommon due to previous exposure to *S. pyogenes*. No IgE antibodies were detected, but at Baseline ≥ 85% of patients had detectable anti-imlifidase IgG.

No neutralising antibody assay was included in the dossier, and to some extent partially justified by a proposed single dose regimen (even though a second facultative dose may be given). Population PKPD modelling did not suggest a clinically significant effect between pre-dose ADA levels and the PD effect of imlifidase at the proposed dose.

Cross-match status and conversion should be monitored to mitigate the risk.

Sample size limitations

There are a limited number of patients who have been treated with imlifidase (in total 139 patients and volunteers in clinical trials) and this is insufficient to identify uncommon and rare AEs.

Comparator limitations

In the target population, there were no comparator controlled studies or studies that referred to a reference population, historical or otherwise, in the Phase II studies. There are limited comparator data available from the placebo groups in the Phase I studies.

Proposed action

Benefit-risk balance

The sponsor has completed Phase I and II studies that have determined the dosing regimen and demonstrated the feasibility of imlifidase in the proposed indication.

The preliminary efficacy data are encouraging for the proposed indication. The safety profile appears to be acceptable, especially given the restrictions of use to major centres only and given the single use regimen (plus one additional dose if required).

The sponsor is conducting Phase III confirmatory trials with paired long-term follow-on studies. These studies have the potential to resolve the current knowledge gaps and would enable a more definite benefit-risk balance to be established.

There are sufficient data to determine a benefit-risk balance that is sufficiently favourable to support provisional registration.

Provisional registration

The provisional approval pathway allows sponsors to apply for provisional registration on the ARTG. It provides access to certain promising new medicines where the public health benefit of immediate or early availability of the medicine outweighs the risk inherent in the fact that additional data are still required.

The sponsor has applied for the provisional approval pathway, and the TGA has made a provisional determination for the indication proposed by the sponsor for this application.

Only Phase II uncontrolled trial data are available and Phase III confirmatory data are not yet available. Thus, provisional registration is therefore the most appropriate regulatory option. The provisional registration reflects the present deficiencies of the data balanced with the public health need.

Indication wording

The sponsor is proposing the following indication:

> *Idefirix has **provisional** approval in Australia for the desensitisation treatment of highly sensitised adult kidney patients with a positive cross match against an available donor prior to kidney transplantation.*
>
> *The use of Idefirix should be reserved for patients who are unlikely to be otherwise transplanted. The decision to approve this indication has been made on the basis of efficacy and safety data, demonstrating enabled kidney transplantation and sustained kidney function in the target population. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*

After careful consideration of the provided data and the public health context, the TGA proposed indication is:

> *Idefirix has **provisional** approval for the desensitisation treatment of highly sensitised adult kidney patients with a positive cross-match against an available deceased donor prior to kidney transplantation.*
>
> *The use of Idefirix should be reserved for patients who are unlikely to be otherwise transplanted. The decision to approve this medicine has been made based on limited data. More comprehensive evidence is required to be submitted.*

Advice from the ACM is kindly requested.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Can the ACM comment on whether there are sufficient data to register Idefirix for provisional registration?

The ACM agreed that there is sufficient safety and efficacy data to support the provisional registration of Idefirix to facilitate transplantation for selected HLA-sensitised transplant candidates.

The ACM noted that long-term data are lacking and that there are no completed Phase III studies. The ACM considers that the long-term outcome data will be important given antibody rebound and established prognostic implications of rejection and donor specific antibodies.

The ACM noted that there are no effective alternative desensitisation approaches for the particularly highly sensitised transplant candidate, which therefore, excludes or significantly delays kidney transplantation for this group.

2. Can the ACM comment on the proposed indication wording including a consideration of living donors?

The ACM noted the indication should be agnostic to donor source as HLA sensitisation affects access to transplantation regardless of donor source. The ACM cannot foresee the source of the organ (deceased versus live donor) affecting the safety and efficacy of imlifidase.

The ACM noted that existing desensitisation approaches are ineffective in living donor transplantations for particularly highly sensitised recipients, and accepted risk tolerances are generally lower in this cohort due to the risks for the living donor. In the Australian context, use of imlifidase is likely to be more feasible in the living donor context due to opportunities for better advanced planning, organ quality and preparation of the recipient.

3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM noted there are currently no effective desensitisation approaches for particularly highly sensitised transplant candidates and that there is substantial individual, societal and health system harms that arise from delayed access to transplantation.

The ACM noted that in the Australian context, transplant clinicians would initially proceed cautiously, gaining experience with lower risk candidates.

The ACM considered that the emergence of machine perfusion may support the application of imlifidase in the deceased donor transplant context.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Idefirix has provisional approval for the desensitisation treatment of highly sensitised adult kidney transplant candidates before transplantation from a donor against whom there is a positive cross-match.*

The use of Idefirix should be reserved for patients who are unlikely to be otherwise transplanted. The decision to approve this medicine has been made based on limited data. More comprehensive evidence is required to be submitted.

Delegate decision

Indication

After review of the evidence and consideration of the advice from the ACM, the following indication was approved:

*Idefirix has **provisional** approval 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 (see Section 5.1 Pharmacodynamic properties, Clinical trials). The use of Idefirix should be reserved for patients who are otherwise unlikely to receive a kidney transplant.*

The decision to approve this medicine has been made based on limited data. More comprehensive evidence is required to be submitted.

The approved indication does not specify whether the donors are deceased or living. Transplants from living donors may be used. This decision was made based on the existing clinical data, and also on the clinical data that will be derived from the ongoing studies.

With regard to confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence), Studies 17 and 19, and their longer-term follow up components (Studies 25 and 20, respectively), do not include living donors. However, given that imlifidase acts in the recipient, and the inherent effect is independent of donor source, a reasonable extrapolation can be made at this stage.

The main difference (between deceased and living donor indications) lies in the benefit-risk balance, that is the benefit may be reduced for living donor transplantation, if reliable and practical alternative desensitisation therapies were available specifically for that donor group. Some potential, alternative therapies (for example, plasma exchange) or approaches (for example, waiting for an immunologically compatible donor) are available, but in the absence of their demonstrated reliability and practicality the benefit-risk balance is insignificantly different when compared to treatment prior to transplantation from deceased donors.

The approved indication was not based on the sponsor-proposed observational study, as no details were available at the time of decision.

The indication wording refers to Section 5.1 of the PI for prescribers to make an informed decision based on clinical data. Given its setting in transplantation medicine, imlifidase will only be used by highly specialised specialist prescribers.

Conditions of registration

The following non-standard conditions of registration were imposed:

Condition 10

Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the six years that would start on the day that registration would commence) must be provided. Specifically, the sponsor must provide

the clinical study reports (CSRs) for studies as specified in the 'Clinical study plan for provisional registration' section of the Idefirix EU-RMP ASA (version 0.2, dated 21 February 2023):

- Study 17-HMedIdeS-14 (Study 14) (expected in fourth quarter of 2023)
- Study 20-HMedIdeS-19 (Study 19) (expected in fourth quarter of 2025)
- Study 20-HMedIdeS-17 (Study 17)

Condition 11

Additional and separate to the confirmatory trial data specified above, the sponsor should provide the clinical study reports (CSRs) for the following studies, once available:

- Study 20-HMedIdeS-20 (Study 20) (expected in fourth quarter of 2030)
- Study 21-HMedIdeS-25 (Study 25)
- An observational study of renal transplant recipients (from deceased or living donors) following desensitisation with imlifidase conducted in Australia.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Idefirix (imlifidase) 11 mg, powder for concentrate for solution for infusion, vial, indicated for:

> *Idefirix has **provisional** approval 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 (see Section 5.1 Pharmacodynamic properties, Clinical trials). The use of Idefirix should be reserved for patients who are otherwise unlikely to receive a kidney transplant.*
>
> *The decision to approve this medicine has been made based on limited data. More comprehensive evidence is required to be submitted.*

Specific conditions of registration applying to these goods

- Idefirix (imlifidase) is to be included in the Black Triangle Scheme. The PI and CMI for Idefirix must include the black triangle symbol and mandatory accompanying text for five years, or the product's entire period of provisional registration, whichever is longer.
- The Idefirix EU [European Union]-risk management plan (RMP) (version 1.0, dated 16 June 2020, data lock point 1 December 2019), with Australia specific annex (version 0.2, dated 21February 2023), included with Submission PM-2022-02499-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports(PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report (revision 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided. Specifically, the sponsor must provide the clinical study reports (CSRs) for studies as specified in the 'Clinical study plan for provisional registration' section of the Idefirix EU-risk management plan (RMP) Australia specific annex (version 0.2, dated 21February 2023):
  - Study 17-HMedIdeS-14 (Study 14) (expected in fourth quarter of 2023)
  - Study 20-HMedIdeS-19 (Study 19) (expected in fourth quarter of 2025)
  - Study 20-HMedIdeS-17 (Study 17)
- Additional and separate to the confirmatory trial data specified above, the sponsor should provide the clinical study reports (CSRs) for the following studies, once available:
  - Study 20-HMedIdeS-20 (Study 20) (expected in fourth quarter of 2030)
  - Study 21-HMedIdeS-25 (Study 25)
  - An observational study of renal transplant recipients (from deceased or living donors) following desensitisation with imlifidase conducted in Australia.
- Laboratory testing & compliance with Certified Product Details (CPD)

  i. All batches of Idefirix (imlifidase) supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  ii. When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

  A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website:

  [for the form] https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescription-medicines

  [for the CPD guidance] https://www.tga.gov.au/resources/resource/guidance/guidance-7-certified-product-details

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Idefirix approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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https://www.tga.gov.au

Reference/Publication #