13 July 2020
EMA/372587/2020 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Idefirix

International non-proprietary name: imlifidase

Procedure No. EMEA/H/C/004849/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| AA | Amino acids |
| ACN | Acetonitrile |
| ADA | Antidrug antibodies |
| ADCC | antibody dependent cell-mediated cytotoxicity |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AEX | Anion exchange chromatography |
| AHEG | Ad hoc expert group |
| AMR | Antibody-mediated rejection |
| API | Active Pharmaceutical Ingredient |
| BBB | Blood brain barrier |
| BLOQ | Below Limit of Quantitation |
| CDC | Complement-dependent cytotoxicity |
| CDCXM | Cell-based complement-dependent cytotoxicity |
| CFU | Colony forming unit |
| CKD | Chronic kidney disease |
| CL | Clearance |
| CMA | Conditional marketing authorisation |
| CNS | Central nervous system |
| cPRA | calculated Panel reactive antibodies |
| CRP | C-reactive protein |
| CSR | Clinical study report |
| CV | column volume |
| Da | Dalton |
| DGF | Delayed Graft Function |
| DP | Drug Product |
| DS | Drug Substance |
| DSA | Donor specific antibodies |
| ECD | Extended Criteria Donors |
| ECG | Electrocardiogramm |
| ECL | Electrochemiluminescence |
| eGFR | Estimated glomerular filtration rate |
| EDQM | European Directorate for the Quality of Medicines |
| EFD | Embryofoetal development |
| EMA | European Medicines Agency |
| ESRD | End-stage renal disease |
| ET | Eurotransplant |

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|---|---|
| EU | European Union |
| FACS | Fluorescence-Activated Cell Sorting |
| FCXM | Flow cytometry crossmatch |
| FMEA | Failure Modes and Effects Analysis |
| FOB | Functional observational battery |
| G | Gram |
| g/L | Gram/Liter |
| GD | Gestation Day |
| h | Hour |
| HAR | Hyperacute rejection |
| HCP | Host cell protein |
| HC DNA | Host cell DNA |
| HLA | Anti-human leucocyte antigen |
| HMW | High Molecular Weight |
| HUT | Highly unlikely to be transplanted |
| HV | Healthy volunteer |
| IdeS | IgG-degrading enzyme of Streptococcus pyogenes |
| IgG | Immunoglobulin G |
| IMP | Investigational medicinal product |
| IVIg | Intravenous immunoglobulin |
| KAS | Kidney Allocation System |
| KDPI | Kidney donor profile index |
| LD | Living Donors |
| LLOQ | Lower limit of quantification |
| LTE | Long-term extension study |
| MAA | Marketing authorisation authorisation |
| MCB | Master Cell Bank |
| MFI | Median fluorescence intensity |
| mM | Millimolar |
| µM | Micrometer |
| MSD | Meso Scale diagnostic |
| nM | Nanometer |
| LOCF | Last observation carried forward |
| OD | Optical density |
| $O_2$ | Oxygen |
| OPTN | Organ Procurement and Transplantation Network |
| O.U. | Optical Units |
| PAES | Post authorisation efficacy study |
| PD | Primary pharmacodynamic |

| | |
|---|---|
| pI | Isoelectric point |
| PIP | Paediatric investigation plan |
| PKPD | Pharmacokinetic-pharmacodynamic |
| PLEX | Plasmapheresis |
| PRA | Panel reactive antibodies |
| PT | Preferred term |
| PVDF | Polyvinylidene difluoride |
| QoL | Quality of life |
| RCB | Research Cell Bank |
| rDNA | Recombinant Deoxyribonucleic Acid |
| RS | Reference standard |
| RWD | Real-World Data |
| SAB | Single antigen bead |
| SAE | Serious adverse event |
| SAS | Safety Analysis Set |
| sc | single chain |
| scIgG | single cleaved IgG |
| SMCA | State Medicines Control Agency under the Ministry of Health of the Republic of Lithuania |
| TEAE | Treatment emergent adverse event |
| TTC | Threshold of Toxicological Concern |
| TTP | Thrombotic thrombocytopenic purpura |
| UF/DF | Ultrafiltration/diafiltration |
| UNOS | United Network for Organ Sharing |
| UTI | Urinary tract infection |
| UV | Ultraviolet |
| vXM | virtual crossmatch |
| WCB | Working Cell Bank |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Hansa Biopharma AB submitted on 5 February 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Idefirix, through the centralised procedure falling within the Article 3(1) and point 4 of Annex I to Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 May 2017.

Idefirix, was designated as an orphan medicinal product EU/3/16/1826 on 12 January 2017 in the following condition: *Prevention of graft rejection following solid organ transplantation*.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Idefirix as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/idefirix

Idefirix was granted eligibility to PRIME on 18 May 2017 in the following indication: *Prevention of graft rejection following solid organ transplantation*.

Eligibility to PRIME was granted at the time in view of the following:

- Given the large number of highly sensitized patients who are not able to receive kidney transplant, a new and effective approach would be needed for the management of these patients. There is no efficient authorised treatment for the cleavage of IgG and therefore the unmet medical need is agreed.
- In phase 2 studies presented, the product showed a significant decrease in serum IgG already within the hour of administration to negligible levels between 24-48 hours. This could allow transplantation of highly sensitized patients with diseased donors.

The applicant applied for the following indication:

*Idefirix is indicated for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor.*

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0229/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0229/2018 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Applicant's requests for consideration*

### Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

### New active Substance status

The applicant requested the active substance imlifidase contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

## *PRIME support*

Upon granting of eligibility to PRIME, Martina Weise was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 29 September 2017. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

*Impact of change of manufacturing site, characterisation and development of drug substance and drug product specifications, tissue distribution and pharmaco/toxicokinetics, toxicology studies and safety margins, plans for reproductive toxicity studies on fertility and pre/post-natal development, proposed clinical development programme for initial marketing authorisation, in particular on the design of study 15-HMedIdes-06, safety, risk management planning and post-authorisation planning, paediatric investigation plan, orphan designation and conditional marketing authorisation.*

## *Protocol assistance*

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 20 September 2018 | EMEA/H/SA/3863/1/2018/PA/SME/PR/III | Elmer Schabel, Romaldas Mačiulaitis and Armando Magrelli (for issues on significant benefit) |

The Protocol assistance pertained to the following quality, non-clinical and clinical aspects:

- Quality: Adequacy of the comparability exercise to support changes in manufacturer and manufacturing process for marketing authorisation application (MAA) assessment. Specification tests and analytical methods for quality control of the active substance (AS) and finished product (FP). Validation plans for validation of the manufacturing process for the AS and FP.
- Non-clinical: Overall acceptability of the non-clinical program to support MAA.
- Clinical: Whether the proposed indication "Pre-transplant treatment to make patients with donor specific IgG eligible for kidney transplantation" reflects the mode of action. Adequacy of the available clinical data package (including one study in 29 healthy volunteers, two completed phase II studies in 18 sensitized CKD patients and two ongoing phase II studies in 35 highly sensitized CKD patients) to support a CMA, and whether the proposed specific obligations (including a long-term extension study (LTE), a PASS, and a Real-World Data (RWD) / registry study) could provide comprehensive data confirming a positive benefit-risk balance in support of a full MA.

## *Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Kristina Dunder

The appointed co-rapporteur had no such prominent role in Protocol assistance relevant for the indication subject to the present application.

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|---|---|
| The application was received by the EMA on | 5 February 2019 |
| The procedure started on | 28 February 2019 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 24 May 2019 |
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 21 May 2019 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 4 June 2019 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 27 June 2019 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 21 December 2019 |
| The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: | |
| – A GCP inspection at two clinical investigator sites in the United States and Sweden between 26 June and 26 July 2019. The outcome of the inspection carried out was issued on. | 6 September 2019 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 7 February 2020 |

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|---|---|
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 13 February 2020 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 27 February 2020 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 30 March 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 16 April 2020 |
| The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on | 30 April 2020 |
| The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on | 26 May 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on | 10 June 2020 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Idefirix on | 25 June 2020 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a revised positive opinion for granting a marketing authorisation to Idefirix on | 13 July 2020 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

The applicant applied initially for approval of Idefirix (Imlifidase) in the following indication:

*Idefirix is indicated for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor.*

### 2.1.2. Epidemiology

Chronic Kidney Disease (CKD) stage 5 is the most severe grade of CKD and is defined as glomerular filtration rate (GFR) < 15 ml/min/1.73 m2. Renal transplantation is the optimal treatment for patients with CKD stage 5 since it increases patient survival and quality of life (QoL).

In 2017, more than 27.000 kidney transplantations were performed in Europe.

According to statistics from the European Directorate for the Quality of Medicines (EDQM), between 40,000 and 45,000 subjects were active on the renal transplant waiting list in the EU on 31-Dec-15. Almost 1,700 subjects in EU died during 2015, while on the waiting list.

More than 1/3 of patients waiting for kidney transplantation are sensitized to a varying extent against potential donor tissue. As many as 15% of all patients on the transplantation waiting list are classified as highly sensitized, defined as calculated panel reactive antibodies cPRA ≥ 80% (6% have a cPRA of 80-98% and 8% have a cPRA of 98-100%) (data from Scientific Registry of Transplant Recipients).

### 2.1.3. Clinical presentation, diagnosis

The target population of Idefirix consists of highly sensitized patients awaiting kidney transplantation, who are highly unlikely to receive a compatible kidney transplant, due to their broad anti-HLA antibody profile. These patients have no compatible living donor.

The antibodies, these patients have, are reactive to the HLA antigens of a potential organ donor, which are referred to as donor-specific antibodies (DSA). Pre-formed DSAs can be caused by the exposure to foreign antigens induced by e.g. during pregnancy, blood transfusions and former organ transplantations. Antibodies against a potential donor can result in a positive cross match test to that donor, which is considered to be a contraindication to transplantation due to the possibility of a hyper acute antibody-mediated rejection (AMR) beginning immediately after reperfusion of the transplant with the worst- case scenario of graft failure and the return to dialysis.

The degree of sensitization is determined by analysing panel-reactive antibodies (PRA) or calculated PRA (cPRA). PRA includes testing of the patient's sera against a panel of 30 to 100 blood donors, while cPRA is a computer-based method to test the patient's antibody profile against > 12,000 potential donors. As many as 15% of all patients on the transplantation waiting list may be classified as highly sensitized, when defined as a cPRA ≥ 80% (6% have a cPRA of 80-98% and 8% have a cPRA of 98-100%).

The probability of finding an HLA-compatible donor for patients with antibodies reacting against a wide range of HLAs is very low. This is true for patients waiting for a deceased donor kidney but also for those considered for living-donor transplantation within a paired donation programme.

Therefore, highly sensitized patients have an extended waiting time for transplantation compared to patients with no or low grade of sensitization. These patients are maintained on dialysis while awaiting an organ offer, which has been shown to have a negative impact on QoL and survival.

### 2.1.4. Management

Clinical practice in handling highly sensitized patients differs between countries, but there is an unmet medical need regardless of the methods available. In clinical practice, when a kidney from a deceased donor is offered, crossmatch tests are performed against all patients on the waiting list. Most of the highly sensitized patients, who are prioritized in many countries, have a positive crossmatch and are therefore not transplanted. The available organs are offered to less sensitized patients with a negative crossmatch or to non-sensitized patients.

To expand the donor pool for highly sensitized patients, these patients are put on separate acceptable mismatch programmes. However, it is estimated by the Applicant, that for about 35% of the most highly sensitized patients (98- 100% cPRA) no available donor will be found in the EU. In the US, the Kidney Allocation System (KAS) is unable to find a suitable kidney for approximately 3000 patients on the waiting lists, according to the Applicant. Kidney exchange programmes are insufficient for the most highly sensitized patients.

Unfortunately, many sensitized patients become delisted due to comorbidity or die while on dialysis instead of becoming transplanted.

Several approaches are used in current clinical practice to make sensitized patients eligible for transplantation. These techniques aim at removing antibodies, e.g. plasmapheresis or immunoadsorption, often combined with B-cell depleting agents (e.g. rituximab and/or bortezomib), immunomodulatory agents (e.g. intravenous immunoglobulin [IVIg]) or complement blockers (e.g. eculizumab). These treatments require repeated dosing for several weeks to months prior to transplantation and are almost exclusively used for living-donor kidney transplantation since deceased-donor kidney transplantations must take place within hours of donor death.

Therefore, faster and more effective methods are needed to rapidly remove antibodies against a potential donor. Such treatment would address the unmet medical need to convert a positive crossmatch into negative and thereby allow deceased-donor kidney transplantation in highly sensitized patients.

There are no medicinal products explicitly approved for enabling renal transplantation in sensitized patients. According to the Applicant, there are no developments in the area of the proposed indication other than further development of extracorporal methods and equipment such as plasmapheresis and immunoadsorption.

### *About the product*

Imlifidase is a recombinant cysteine protease and IgG endopeptidase derived from the IdeS molecule from *Streptococcus pyogenes*, developed for pre-treatment of highly sensitized patients diagnosed with CKD and planned to be transplanted. Imlifidase is expressed in Escherichia coli, Imlifidase is monomeric, does not form any disulphide bridges, and is not subject to any post-translational modifications, such as glycosylation.

The drug product is manufactured by Baxter. It is delivered as a freeze-dried (lyophilised) powder to be reconstituted with water for injection prior to infusion.

The proposed clinical use of imlifidase initially applied for is "*desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor.*"

The applicant initially applied to recommend the dose of Idefirix is 0.25 mg/kg administered as a single dose preferably within 24 hours prior to transplantation. The treatment is not intended to be repeated after transplantation.

## *Type of Application and aspects on development*

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data through the completion of the long-term follow-up Study 14. In addition, the applicant intends also to conduct a post-approval efficacy study that would be an open-label, non-randomized study in Europe and USA in patients with DSA aiming at assessing the efficacy and safety of imlifidase in comparison to historical controls. Finally, the applicant intends to conduct a non-interventional prospective 5-year observational registry to evaluate the safety and outcome of using in routine clinical practice.
- Unmet medical needs will be fulfilled, as the target population for imlifidase is highly sensitized patients waiting for kidney transplantation, who, due to their broad anti-human leucocyte antigen (HLA) antibody profile, are highly unlikely to receive a compatible kidney transplant. For living donor transplantations, desensitization methods are available for successful transplantation. However, in the case of deceased donor kidneys, these methods are usually not feasible due to the very limited time available. Most desensitisation treatments require repeated dosing prior to transplantation and are almost exclusively used for living-donor kidney transplantation since deceased-donor kidney transplantations must take place within hours of donor death. The applicant estimated a delay in the authorisation by 5 years in case supplemental safety data would be required to support the marketing authorisation. During this 5-year period, the applicant estimates that 10,000-20,000 patients with donor specific IgG who might have been made eligible for kidney transplantation through imlifidase treatment, would have missed an opportunity to receive a kidney transplant. The limited window of opportunity during which intervention may be effective may therefore have passed for a substantial number of patients with this disease, and for all these patients, they would likely have been consigned to continued dialysis and deterioration of their condition. Since approximately 5% of patients are removed from transplant waiting lists each year due to death or morbidity, and with a 5-year delay, the applicant considers that a substantial number of patients (500+) would have lost their chance for a potentially life changing transplantation.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 11 mg imlifidase as active substance. The active substance imlifidase contained in the medicinal product Idefirix is a cysteine protease derived from an immunoglobulin G (IgG)-degrading enzyme of Streptococcus pyogenes (IdeS) and expressed in *E. coli*. Other ingredients are: mannitol, polysorbate 80, trometamol, disodium edetate dihydrate, hydrochloric acid.

The finished product is supplied in a vial (Type I glass) with a stopper (bromobutyl rubber) and flip off seal (aluminium).

After reconstitution, each mL of concentrate contains 10 mg imlifidase. The concentrated solution is further diluted into 50 mL of 0.9% sodium chloride infusion solution. The sterile water for injections (sWFI) and the 0.9% sodium chloride are not supplied with the imlifidase finished product.

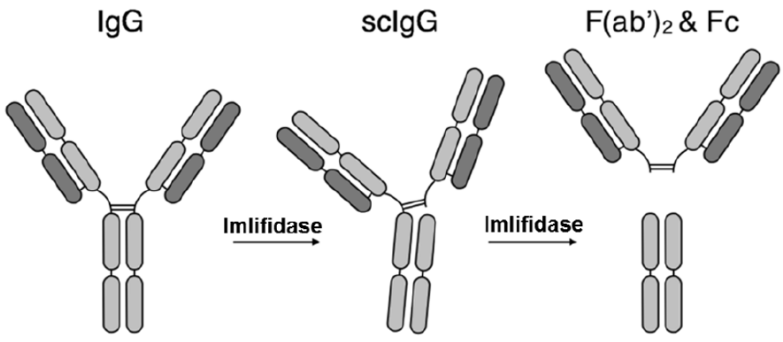
### 2.2.2. Active Substance

#### *General information*

The active substance (AS) imlifidase (INN) is a recombinant IgG degrading enzyme originating from Streptococcus pyogenes (IdeS). It is a 35 kDa cysteine protease and IgG endopeptidase from S. pyogenes expressed in *Escherichia coli*.

Imlifidase specifically cleaves human IgGs just downstream of the hinge region in a two-step procedure. It first cleaves one of the heavy chains generating a single cleaved IgG molecule (scIgG) which introduces a conformational change in the IgG. Secondly, the remaining heavy chain is also cleaved leading to the release of a F(ab')2 fragment and a dimeric Fc fragment (Figure 1. Imlifidase thus efficiently neutralises Fc-mediated activities of IgG including leukocyte recruitment, Fc-mediated phagocytosis, antibody dependent cell-mediated cytotoxicity and complement activation.

**Figure 1 Activity of imlifidase**




The proteolytic activity and target specificity of imlifidase is dependent on both physical interactions with the IgG Fc-domain and on the recognition of a target sequence located C-terminal from the IgG hinge region where imlifidase cleaves after the Gly236 residue.

Imlifidase is a protease that specifically neutralises all four human subclasses of soluble and bound IgG (IgG1, IgG2, IgG3 and IgG4). Imlifidase rapidly cleaves and substantially reduces the load of IgG including those reactive to donor specific antigens, thereby reducing the serum levels of pathogenic

donor specific antibodies (DSA) to a level where transplantation is possible without damage to the graft.

## *Manufacture, characterisation and process controls*

Description of manufacturing process

The active substance is expressed in *E. coli* as a recombinant protein that originates from *Streptococcus pyogenes*. The cell substrate used for expression of imlifidase is based on an *E. coli* strain suitable for high-level protein expression using an induction system. The nucleotide sequence coding for the imlifidase protein originates from the *S. pyogenes* strain. The nucleotide sequence of the coding region of the gene of interest and associated flanking regions have been verified by DNA sequencing.

The manufacturing of imlifidase active substance includes two process stages: the upstream process for cell culture and harvest, followed by the downstream process for protein release and purification.

The upstream process starts with thawing of WCB as inoculum. Cell expansion and cell production proceeds. At a target optical density (OD), imlifidase production is induced. The fermentation process is terminated and the cells are harvested.
The downstream process starts with cell disruption for protein release, followed by filtration. The purification process continues with a number of chromatography steps. The resulting protein solution is concentrated, filtrated and filled in bottles for storage at -80°C. Hold times are reported and are considered appropriately supported by respective stability data.

**Control of materials**

A two-tiered cell bank system has been established. The program applied for characterisation of the master cell bank (MCB) and working cell bank (WCB) is considered adequate to identify the relevant phenotypic and genotypic markers. Acceptable specifications for MCB and WCB as well as an appropriate protocol for establishment of future WCBs have been provided. Monitoring of cell bank stability has been acceptably explained. An acceptable plasmid retention during the manufacturing process has been confirmed during process validation.

**Process controls**

Detailed information has been provided on the active substance manufacturing process. Process parameters and controls have been provided including the respective acceptance criteria.

Batch size and scale has been defined. Inoculation, cell expansion, production and cell harvest are considered critical steps during the upstream process, chromatographic operations and filtration steps are considered critical steps during the purification process. All in-process controls (IPCs) performed at the critical steps during upstream and downstream process are listed together with their acceptance criteria and are found in agreement with information provided. The acceptance criteria/action limit concept applied for bioburden and endotoxin testing is considered acceptable.

Critical quality attributes (CQAs) of imlifidase have been explicitly defined. Appropriate information is available to support the link between CQAs and the critical process parameter as determined for the active substance purification process.

The link between the proposed critical steps, critical process parameters (CPP) and IPCs determined for the purification process as well as the identified CQA is based on Failure Mode and Effects Analysis (FMEA). Based on the FMEA, the influence of potential CPP variations on the CQA was evaluated. For each CPP the Proven acceptable range (PAR) was tested experimentally. All the identified CPPs

together with the respective normal operating range (NOR) have been included. This is considered appropriate.

**Process validation and/or evaluation**

To demonstrate suitability and robustness of the imlifidase manufacturing process to consistently produce active substance with its pre-determined specifications and the appropriate quality attributes, a prospective process verification study has been conducted using several consecutive imlifidase batches representing the intended commercial process. Appropriate validation data including data for all process parameters and tests defined have been provided.

***Manufacturing process development***

The manufacturing process evolved from the lab scale process to the initial process as well as Process 1 since 2009. All clinical studies that have been initially filed have been performed using Process 1 AS material. At D120, imlifidase AS manufactured by Process 2 has not been used in any of the clinical studies. In 2016, Process 1 has been transferred and substantial process optimisation resulted in Process 2.
Process optimisation from Process 1 (clinical) to Process 2 (commercial) comprises changes in both upstream and downstream process. All performed process changes have been explained and sufficiently assessed with regard to their impact on the product quality.

To compare Process 1 and Process 2 materials, one Process 1 batch and two Process 2 batches have been included in an initial comparability study. The comparability exercise comprises comparative analytical testing, comparative characterisation and stability studies. In the initial file, comparability at active substance level has not been sufficiently demonstrated. Moreover, the frozen FP formulation used in clinical and most of the non-clinical studies has been replaced by a lyophilized FP formulation. However initially, no comparability study were performed at the finished product level. Due to the differences of the active substances and the qualitative composition of the formulations resulting from the changes to the FP manufacturing processes, the relevance of the non-clinical and clinical data generated with process 1 material for the product to be marketed was in question. This has been raised as a multidisciplinary Major Objection at D120.

An additional, extensive comparability study has been performed at active substance level comparing Process 1 and Process 2 imlifidase materials. Since process 1 active substance was not available at the time of the comparability study, process 1 finished product has been used instead as an representative of the active substance. The Applicant's conclusion to consider process 1 finished product material being valid for use in the comparability study is endorsed.

Comparison of release data and extensive characterisation, including identification and characterisation of imlifidase variants and impurities, discloses the main difference between Process 1 and Process 2 imlifidase active substances. Process 1 imlifidase active substance contains much higher amounts of an inactive variant whereas Process 2 imlifidase appears more pure. As regards biological activity and due to the presence of the inactive impurity, the potency of Process 1 imlifidase is lower than that of Process 2 imlifidase.

Extensive comparability tests were also performed for the Process 1 and Process 2 material at the finished product level. As expected, the finished products of Process 1 and Process 2 are not fully comparable. The impurity profile with respect to the inactive variant is different and the biological activities are not comparable.

Due to the observed differences at quality level, an impact on safety and efficacy profile cannot be excluded and additional toxicological and clinical studies with the commercial finished product were

necessary to address the residual uncertainty and confirm comparability. Additional toxicological and clinical studies were performed and demonstrate comparability between process 1 and process 2 imlifidase. For further details on these studies reference is made to the pre-clinical and clinical parts of the CHMP assessment report.

**Characterisation**

Imlifidase is a cysteine protease derived from an immunoglobulin G (IgG)-degrading enzyme of *Streptococcus pyogenes* (IdeS) that specifically cleaves IgG in the hinge region between glycine residues 236 and 237 in both heavy chains.

Characterisation of imlifidase has been performed using batches representative for the proposed commercial Process 2.

Comprehensive structural and physiochemical characterisation data have been presented for imlifidase Process 2 material.

The biological activity of imlifidase active substance has been addressed.

As regards post-translational modifications and impurities, product-related impurities in Process 2 imlifidase active substance have been identified and characterised using a set of orthogonal analytical methods.

Minor impurities have also been characterised by a set of orthogonal analytical methods and/or deduced from theoretical literature information.

## *Specification*

The active substance specifications cover tests for appearance, identity, purity and impurities, potency, content, and microbiological quality of imlifidase active substance. Due to the limited number of AS batches forming the data base for the acceptance criteria of the current specification the Applicant is recommended to re-evaluate the proposed limits for some of the tests once additional commercial AS batches are available.

Analytical methods

The analytical methods employed for active substance release testing are mostly in-house methods complemented with compendial methods, for which sufficiently summarised descriptions have been provided. The non-compendial analytical procedures used for batch release testing of imlifidase active substance have been appropriately validated in accordance to ICH Q2(R1) and validation reports have been provided.

Batch analysis

Batch analysis data of imlifidase active substance batches manufactured according to the current Process 2 and former Process 1 have been provided. Batch results are consistent between batches of the defined process and demonstrate that all manufacturing batches met the acceptance criteria of the specification in force at the time of release. In addition, satisfactorily updated batch data in line with the revised active substance specification and in particular including the revised impurity profile have been provided.

Reference standard

The current in-house reference standard has been produced according to Process 2. Characterisation of the current RS is considered sufficient. The proposed annual re-testing of current RS is considered acceptable.

Container Closure

An acceptable specification has been provided and conformance with Ph. Eur. requirements of primary packaging materials has been confirmed.

### *Stability*

The stability protocols for Process 2 material includes long-term testing at -80°C ± 10°C, intermediate testing at -20°C ± 5°C, and accelerated testing 5°C ± 3°C. Additional stability studies at elevated temperatures at 25°C ± 2°C/60% ± 5% RH (with or without methionine) and 40° ± 2°C/75% ± 5% RH have been conducted.

Analytical test procedures used in the stability studies are a subset of analytical methods used for active substance release. The stability protocol for future testing includes also testing of the impurity profile and is considered acceptable.

Based on the stability data provided the claimed shelf-life for the active substance is considered acceptable.

## 2.2.3. Finished Medicinal Product

### *Description of the product and pharmaceutical development*

Description and composition of the finished product

Imlifidase for injection is a powder for concentrate for solution for infusion supplied in a glass vial with bromobutyl rubber lyophilisation stopper containing 12 mg imlifidase per vial (includes 1 mg overfill).

Imlifidase finished product (FP) is reconstituted prior to administration in 1.2 mL sterile water for injections (sWFI) resulting in a 10 mg/mL concentrated solution. The extractable volume is 1.1 mL (corresponding to 11 mg of imlifidase active substance) per vial. The concentrated solution is further diluted into 50 mL of 0.9% sodium chloride infusion solution. The sWFI and the 0.9% sodium chloride are not supplied with the imlifidase finished product.

The overfill of 1 mg imlifidase per vial in order to meet the label claim has been adequately justified by data.

Pharmaceutical development

The development section of the finished product contains satisfactory information with respect to the quality target product profile (QTPP), CQAs and CPPs. The CPPs and IPCs with acceptance criteria have been also provided.

For commercial purposes the frozen formulation (FP Process 1) used for Phase 1 and Phase 2 clinical trials has been replaced by the more user-friendly lyophilised formulation (FP Process 2). The qualitative and quantitative choice of the components of the lyophilised finished product has been sufficiently described. Development of the lyophilised formulation and the program for the freeze-drying process have been described in sufficient detail.

The finished product manufacturing process developed for commercial finished product manufacturing comprises thawing of the active substance at room temperature, compounding by adding excipient solutions followed by a bioburden reduction filtration into a holding vessel. The active substance is heat labile. Terminal sterilisation is therefore not feasible. The bulk solution is in-line sterile filtered before

being filled aseptically into sterile, depyrogenated vials. This is followed by a lyophilisation step and capping of the vials. The manufacturing process development section sufficiently described the selection of the lyophilization process.

The manufacturing process of the frozen imlifidase finished product used in Phase 1 and Phase 2 clinical trials was also addressed. Clinical data were only available for frozen finished product with active substance of Process 1. The commercial finished product formulation was not supported by sufficient comparability data nor by clinical development. This resulted in a Major Objection.

Meanwhile extensive comparability tests were performed for the Process 1 and Process 2 finished product covering evaluation of the changes in the composition, dosage form and manufacturing as well as comparison of batch release data, impurity profiles, higher order structure, biological activity and temperature stressed samples. As expected, the finished products of Process 1 and Process 2 are not fully comparable. The impurity profile with respect to the inactive variant is different and the biological activities are not comparable.

Due to the observed differences between frozen and lyophilised finished product, an impact on safety and efficacy profile could not be excluded and additional toxicological and clinical studies with the commercial finished product were necessary to address the residual uncertainty and confirm comparability. Additional toxicological and clinical studies were performed and demonstrate comparability between process 1 and process 2 imlifidase. For further details on these studies reference is made to the pre-clinical clinical part of the CHMP assessment report.

Sufficient evaluation of extractables/leachables has been presented.

A compatibility study was performed with two batches of reconstituted and then diluted finished product in low and high concentrations. In-use stability was demonstrated for 24 hours at 2°C - 8°C and protected from light; 4 hours storage of the 24 hours may be at 25°C. The Applicant demonstrated that at the end of in-use storage the diluted finished product is sterile.

## *Manufacture of the product and process controls*

Baxter Oncology GmbH in Halle, Germany is responsible for production of the lyophilised finished product, primary packaging and quality control testing. For the manufacturing sites valid manufacturing authorisations and GMP certificates covering the responsibilities listed are available in the EudraGMPD database.

The non-standard manufacturing process of imlifidase finished product has been sufficiently described. The manufacturing process comprises of the following steps: thawing of the active substance, compounding of the finished product solution, bioburden reduction filtration, in-line sterile filtration and aseptically filling into vials followed by lyophilization, capping, outer decontamination, visual inspection and labelling and packaging. The critical steps of the lyophilized finished product are sufficiently controlled.

A flow diagram representing an overview of the manufacturing steps and the in-process controls has been provided.

**Process controls**

The quality of imlifidase finished product and the consistency of manufacturing steps are monitored by in-process controls throughout the process. A flowchart of the manufacturing process showing the in-process controls (IPCs) and at which stages each test is performed has been provided.

Acceptance criteria have been established at process steps to monitor the consistency of the manufacturing process and to ensure that an investigation is conducted if limits are not met. Acceptance criteria must be met in order for the finished product to be released. Acceptance criteria have been established based on batch data collected during process development as well as results obtained from the process validation studies and are acceptable.

**Process validation**

Process validation data has been provided for three validation batches using different active substance batches. The batch sizes cover the theoretical batch size mentioned in the batch formula.

The presented validation studies are sufficient to demonstrate acceptable manufacturing process performance resulting in a finished product of consistent quality. The validation section includes all manufacturing steps with mixing study, blending study, hold time studies, line flush study, lyophilisation mapping study, filter challenge study and media fill studies.

Results of three media fill runs have been presented.

## *Product specification*

The finished product specifications have been developed as per ICH Q6B guidelines and cover appearance, identity, properties, assay, purity and impurities, potency, and microbiological quality of imlifidase finished product.

The available batch data are limited. Therefore, the commitment that the limits will be re-evaluated when additional finished product batches have been manufactured is endorsed.

The Applicant's conclusion on elemental impurities (ICH guideline Q3D) is accepted.

**Analytical procedures**

The descriptions for the non-compendial analytical procedures provided are sufficient. The non-compendial analytical procedures used for batch release testing of imlifidase finished product have in principle been validated in accordance to ICH Q2(R1).

**Batch analysis**

Batch results have been provided for several batches of the frozen finished product with process 1 active substance and several batches of the lyophilized finished product.

The batch results meet the acceptance criteria per the specification in place at time of batch release and are consistent between the batches of each finished product presentation. Additional results in accordance with the requested changes of the finished product specification have been added for the GMP batches of the lyophilized finished product.

<u>Reference standards or materials</u>

The same reference standards are used for release and stability testing of imlifidase active substance and finished product.

Container closure system

The primary packaging of the finished product consists of a 2 mL colourless Type I tubular glass vial and a 13-mm bromobutyl rubber lyophilization stopper. The stoppers are sealed with 13-mm aluminium cap with plastic disc.

The provided specifications together with the quality certificates of the suppliers of the packaging materials are sufficient to describe the quality of the packaging components.

## *Stability of the product*

A shelf life of 12 months when stored at 2°C - 8°C is claimed for the finished product. Seven batches have been included in the stability program. Data for three process validation batches, a clinical batch manufactured in accordance with the proposed commercial process and an additional GMP batch planned for clinical trials are presented. An engineering/toxicology batch and a laboratory batch have been added both as supportive batches. The batches have been stored at long-term storage conditions 2-8°C. All batches are also stored at -15 to -25°C and at accelerated conditions of 25°C/60%. Stress conditions of 40°C/75% RH are applied on 6 batches.

The stability protocol covers all necessary tests and defines test intervals in accordance with the ICH Q5C guideline.

The primary packaging as described has been used for the stability batches. The stability protocol for future testing has been amended to include the testing of the impurity profile in line with the requested updated finished product specification.

Stability data for up to 24 months at long term conditions of 2-8°C is available. Based on these stability data the proposed shelf-life of 1 year at 2°C - 8°C is acceptable.

The Applicant is recommended to repeat in-use stability testing using the revised finished specifications with samples at the end of the finished product's proposed shelf-life. The compatibility with saline bags, infusion assemblies, different materials or vendors of the filters, and syringes used for delivery to the saline bags will be evaluated.

The same tests as employed in the previous in-use study will be used again. The revised specification proposal (as approved at time of the Marketing Authorisation approval) will be considered in adaptation of the protocol.

Results from this study will be submitted together with the next update of the stability data.

Based on the stability results the claimed shelf life of 12 months when stored at 2°C - 8°C for the finished product is acceptable.

After dilution chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2-8°C and for 4 hours at 25°C during this period. From a microbiological point of view, unless the method of reconstituting and dilution precludes the risk for microbial contamination, the product should be used immediately. If not used immediately, in-use storage conditions are the responsibility of the user. The solution should be stored protected from light.

The precaution statement in the SmPC that the solution for infusion is to be used in conjunction with a sterile, inline, non-pyrogenic, low protein binding filter (pore size of 0.2 µm) is supported by the compatibility study. The statement that the finished product should be stored in the original container to protect it from light is justified by photostability testing results in accordance with ICH guideline Q1B.

### *Adventitious agents*

Microbiological control has been adequately explained throughout the dossier and comprises testing of cell banks, use of controlled raw and starting materials, process steps designed to remove microorganisms if present, and testing of intermediates and product.

No animal- or human-derived materials are used in the manufacturing process of imlifidase. Due to the usage of prokaryotic cells no viral contamination is expected. Furthermore, the TSE risk is neglectable. No concerns are raised regarding the adventitious agent safety evaluation.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

*Active substance*

Overall, sufficient detail has been provided with regard to the active substance manufacturing process, process description and process controls. Process validation is satisfactory, demonstrating the consistency of the process.

The control strategy as such is considered satisfactory. Control of the active substance at release and during stability studies is deemed adequate taking into account the limited available batch data.

Based on comprehensive characterisation data and based on the established link between CQAs and CPPs for the imlifidase manufacturing process, conclusion on suitable parameters for the active substance specification, especially for the profile of product related substances/impurities is possible.

In general, for the active substance, a meaningful specification has been established. The Applicant is recommended to re-evaluate the active substance specifications when more active substance and finished product batches have been manufactured.

*Finished product*

Also, for the finished product, sufficient detail has been provided with regard to the manufacturing process, process description and process controls. Process validation is satisfactory.

Degradation products have been included in the finished product specification including numerical limits. Since the data base for setting the specification limits is limited, the Applicant is recommended to re-evaluate the limits when additional finished product batches have been manufactured.

The Applicant's proposal of a shelf-life of 12 months at long term conditions of 2-8°C based on real-time data in accordance with the revised shelf-life specification is acceptable.

*Comparability of Processes*

Besides an initial comparability study comprising comparative analytical testing, comparative characterisation and stability studies, an additional, extensive comparability study has been performed at the active substance level. The studies revealed the main difference between Process 1 and Process 2 imlifidase active substances. Commercial Process 2 imlifidase active substance is considerably purer and has a higher biological activity.

Extensive comparability tests have been also performed at the finished product level covering evaluation of the changes in the composition, dosage form and manufacturing. As expected, the finished products of process 1 and process 2 are not fully comparable. The impurity profile with respect to the inactive variant is different and the biological activities are not comparable.

In summary, due to the observed differences at quality level, that process 2 material is purer and 2-times more potent than process 1 material, an impact on safety and efficacy profile could not be

excluded. Additional toxicological studies demonstrate comparability between process 1 and process 2 imlifidase. *In vitro* PD data and results of a new PK/PD study using process 2 material show that IgG degradation *in vitro* (using human plasma) and *in vivo* is largely comparable. Because of these findings and due to the fact that imlifidase is highly specific for degrading IgG and no off-target effects have been identified or can be expected, it is concluded that the clinical performance of the products from two different processes is expected to be similar.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality module of the application is appropriately structured and contains overall the expected information. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. From a quality point of view, Idefirix is considered approvable.

### 2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends some points for further investigation.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

Imlifdase is a recombinant cysteine protease from *Streptococcus pyogenes*. The protein is expressed in *E. Coli*.

Initially, the imlifidase drug product used for clinical studies was supplied as a frozen sterile concentrate for solution for infusion (Process 1). In this process, an inactive isomer of imlifidase was detected. The drug product intended for marketed use is a lyophilized powder for concentrate for solution for infusion (Process 2). The inactive isomer was removed and the new material is displaying higher potency. The majority of the primary pharmacodynamics studies conducted during the non-clinical development of imlifidase were performed with material originating from Process 1. A series of bridging studies were conducted with material from Process 2.

### 2.3.2. Pharmacology

#### *Primary pharmacodynamics*

It has been published that IdeS specifically neutralizes IgG both *in vitro* and *in vivo* (von Pawel-Rammingen et al., 2002; Wenig et al., 2004; Vincents et al., 2004). It cleaves the heavy chain of IgG in the lower hinge region and thereby generating one $F(ab')_2$ and one Fc-fragment. The proteolytic activity of the enzyme is dependent on both physical interaction with the IgG Fc-domain (CH2 and CH3) and on the recognition of the target sequence (e.g. Glu-Leu-Leu-Gly236-Gly-Pro in human IgG1) located just C-terminally of the IgG hinge region in which is cleaved after the Gly236 residue (Agniswamy et al., 2004;Wenig et al., 2004 and Vincents et al., 2004). Published studies indicate that IdeS has full enzymatic activity on IgG from human (von Pawel-Rammingen et al., 2002) and rabbit

(Johansson et al., 2008; Yang et al., 2010) whereas pig, mouse, rat, sheep, cynomolgus monkey, rhesus macaque and common marmoset IgG are only partially cleaved (Agniswamy et al., 2004).

In order to establish the mode of action primary pharmacodynamic *in vitro* and *in vivo* studies in dogs, rabbits and with serum samples and IgGs of various species have been performed by the applicant.

**Table 1 Overview of performed pharmacodynamic studies with imlifidase.**

| Type of Study | Test System | Method of Administration | Study Number | Imlifidase material |
|---|---|---|---|---|
| Primary PD data from *in vitro* investigations | | | | |
| Effect on various IgGs from different species | Different species, serum and purified IgGs | *In vitro* | 2012-003<br>2012-025<br>2015-054<br>2018-034R | Process 1<br>Process 1<br>Process 1<br>Process 2 |
| Effect on IVIg and the impact of ADA | IVIg | *In vitro* | 2016-046<br>2018-091R<br>2017-241R | Process 1<br>Process 1& Process 2<br>Process 1& Process 2 |
| Effect on IgG-BCR | Human cells and cell lines | *In vitro* and *ex vivo* | 2012-009<br>2013-012<br>2015-010 | Process 1<br>Process 1<br>Process 1 |
| Effect on IgG, PoC for desensitization | Human serum/mouse cells | *In vitro* | 2014-015 | Process 1 |
| Mode of action of scIgG | Human serum, cells and cell lines | *In vitro* | 2013-007<br>2016-010 | scIgG generated using different imlifidase material Process 1 |
| Effect on HLA (comparison of processes) | Human serum | *In vitro* | 2018-047R | Process 1 & Process 2 |
| Potency (comparison of processes) | Human IgG1, serum and anti-CD20 | *In vitro* | 2017-055 | Process 1 & Process 2 |
| Extended cleaving (comparison of processes) | IVIg | *In vitro* | 2018-073R | Process 1 & Process 2 |
| Effect on IgG: $C_{max}$ vs AUC (comparison of processes) | Human serum | *In vitro* | 2018-010R | Process 1 & Process 2 |
| Effect on IgG (MABEL and MED) | Human/rabbit serum | *In vitro* | 2012-002 | Process 1 |
| Primary PD data from *in vivo* investigations | | | | |
| Effect on IgG; $F(ab')_2$ and Fc kinetics | Rabbit and dog | IV | 2012-022 | Process 1 |
| Effect on IgG, single dose | Rabbit | IV | 2012-004 | Early imlifidase material similar to Process 1 |
| Effect on IgG, single dose | Rabbit | IV | 2018-042R | Process 1 & Process 2 |
| Effect on IgG, weekly dosing | Rabbit | IV | 2012-006<br>2012-011[a] | Process 1<br>Process 1 |
| Effect on IgG, daily dosing | Rabbit | IV | 2016-003<br>2016-062 | Process 1<br>Process 1 |

| Type of Study | Test System | Method of Administration | Study Number | Imlifidase material |
|---|---|---|---|---|
| Effect on IgG, daily dosing, pregnant animals | Rabbit | IV | 2017-004R<br>2017-181R[a] | Process 2<br>Process 2 |
| Effect on IgG (dog only) | Dog | IV | 2012-007<br>2012-012[a] | Process 1<br>Process 1 |

[a]PD evaluated as part of GLP compliant studies

***In vitro* PD studies**

***Cleavage of IgGs from different species***

In order to establish the mode of action, primary pharmacodynamic (PD) *in vitro* and *in vivo* studies in dogs, rabbits and with serum samples and purified IgGs of various species have been performed by the applicant.

In line with published literature, imlifidase was fully active on all IgG subclasses of sera and purified IgGs from human and rabbit. In contrast, IgGs from mouse, rat, dog, cynomolgus monkey, rhesus macaque, and common marmoset were only partially cleaved. In Beagle dogs, imlifidase cleaved some but not all IgG subclasses, therefore, a substantial proportion of dog IgG was not cleaved into $F(ab')_2$- and Fc-fragments. Hence, rabbits were considered as the most relevant species for further toxicity testing whereas dog studies can be seen as supportive. Results are based on non-quantitative SDS PAGE analyses and ELISA/ECL methods. An ELISA has been established to quantify imlifidase activity in dog serum, however, it turned out that this ELISA is not able to quantify all IgG subclasses. However, published studies also indicate that IdeS has full enzymatic activity on IgG from human (von Pawel-Rammingen et al., 2002) and rabbit (Johansson et al., 2008; Yang et al., 2010) whereas pig, mouse, rat, sheep, cynomolgus monkey, rhesus macaque and common marmoset IgG are only partially cleaved (Agniswamy et al., 2004). Therefore, the provided experiments can be considered as sufficient to conclude on species differences and are in line with published data.

***IVIg cleavage by imlifidase and the impact of ADA (study 2016-046)***

In order to address the neutralizing capacity of ADAs on imlifidase, ADA levels and their neutralizing capacity in commercially available IVIg brands (Octagam, Privigen, and Gamunex) were evaluated by SDS PAGE and an immuno assay (IdeS ImmunoCAP) and related to the cleaving activity. ADA ranges from 19-40 mg/L were determined. For comparison, the normal ADA level in the population ranges between <2 – 91 mg/L (Winstedt et al., 2015). Despite differences in ADA amounts (Octagam batches exhibited the highest amount of ADAs (up to 40 mg/mL)), no differences in imlifidase cleaving activity between batches could be noted. During clinical trials with imlifidase, a reference group (n = 130) was screened with the IdeS ImmunoCAP assay prior to start of the 11-HMedIdeS-01 study. Ten out of 130 subjects had ADA below the cut-off (2.0 mg/L). The median level of ADA was 6.1 mg/L (range: 2.0–78.0 mg/L; n = 130) with the 80% percentile at 15 mg/L. During the 11-HMedIdeS-01 study, 78 healthy subjects were screened for ADA and all had detectable IgG against IdeS. The median level of ADA was 10.6 mg/L (range: 2.1–90.8 mg/L) and 28% of the tested individuals had ADA titres over 15.0 mg/L. It could be demonstrated that ADAs in human serum have neutralizing capacity. Removing ADAs from IVIg preparations resulted in a major impact on the concentration of imlifidase needed to accomplish the intermediate scIgG product but had only minor impact on the concentration of imlifidase needed to accomplish complete cleavage to the end products i.e. $F(ab')_2$ and Fc fragments. Furthermore, it was demonstrated in Western blot experiments that ADA extracted from IVIg bind to

both the active and inactive isomer of imlifidase. It has also been shown that complete cleavage of all IgGs is achieved at similar concentrations independent of ADAs (> 7µg/mL). Therefore, it was concluded that it is important to reach sufficiently high levels *in vivo* to completely cleave all IgGs and to avoid circulation of scIgG, which has been shown to have Fc-mediated activity.

***Effect on IgG - Proof of concept for desensitization (study 2014-015)***

Proof of concept studies have been performed to investigate if treatment with a clinically relevant dose of imlifidase can turn a positive cross-match test into a negative using serum from sensitized patients and to investigate the correlation between serum levels of total IgG and levels of IgG specific to HLA class I and II. Human serum samples treated with imlifidase were analysed for intact IgG using a validated ELISA assay to monitor imlifidase efficacy in serum samples from the phase I clinical study. Single antigen bead (SAB) analyses were used to characterize anti-HLA antibodies from serum samples before and after imlifidase treatment against a panel of MHC class-I and -II antigens (One Lambda). The sera were also tested and scored for reactivity in a complement-dependent cytotoxicity (CDC) screen test on T and B cells from 23 donors by using validated methods. The data showed that imlifidase treatment could rapidly and substantially reduce the level of total IgG. Furthermore, this activity was directly reflected as a reduction of specific and/or broad-reactive anti-HLA IgG in serum from these patients. SAB analyses clearly demonstrated that imlifidase treatment could reduce the level of IgG antibodies directed against all HLA tested positive in serum from all analysed patients. Imlifidase and placebo treated serum from patients were further subjected to a sera-screen CDC test against a panel of T-cells (i.e. cells enriched for CD8+) and B cells (i.e. cells enriched for MHC class-II+) from selected and well characterized donors. The reduction in the level of functional IgG after imlifidase treatment was directly reflected in the CDC tests against T and B cells (CDC-CXM) from hypothetical donors where the capacity of imlifidase to turn a positive cross-match to negative was demonstrated. Furthermore, serum collected from healthy subjects before treatment with 0.24 mg/kg imlifidase reacted strongly in CDC-CXM assays against mouse target cells, whereas serum collected 2 and 24 hours after imlifidase-treatment were negative, which further strongly suggests that imlifidase has the capacity to turn off cytotoxic antibody activity against donor cells. Based on these data it can be concluded that imlifidase treatment just prior to transplantation has the potential to desensitise highly sensitized patients and thereby allowing transplantation and avoiding an AMR.

***Mode of action of scIgG (as mediator of ADCC, CDC, and phagocytosis)***

The mode of action of the scIgG cleavage product was investigated via 3 *in vitro* models based on rabbit IgG as a substrate (study 2013-007). Human effector cells (NK-cells, monocytes, macrophages etc.) can kill IgG-opsonized targets (i.e. antigen expressing cells, bacteria and virus) either by antibody-dependent cellular cytotoxicity (ADCC) or FcγR-binding followed by phagocytosis. Furthermore, antibodies per se can kill cells by CDC without the need of effector cells (generation of the membrane attack complex). These antibody-mediated functions were used to evaluate if scIgG, generated upon imlifidase cleaving the first heavy-chain of IgG, has similar or reduced capacity to mediate these phagocytic and cytotoxic effects compared to intact IgG and $F(ab')_2$-fragments. In these experiments fully cleaved material was generated with high concentrations of his-tagged native IdeS, and scIgG was generated using a carefully selected concentration of a his-tagged variant of IdeS with attenuated activity. The His-tag was used in order to remove the enzyme from the treated antibodies. It could be shown that imlifidase treatment resulting in the end-products ($F(ab')_2$ and Fc) abrogates phagocytosis, ADCC and CDC. A difference was also observed between intact IgG and scIgG as mediators in phagocytosis and both antibody-dependent cytotoxicity and complement-dependent cytotoxicity. scIgG attenuates Fc-mediated capacity compared to intact IgG. It should be noted that there was a contamination of intact IgG in the scIgG preparation and this might have accounted for effects seen when evaluating the scIgG antibody.

A second study focusing on scIgG of human origin in assays in clinical use in the transplant setting was conducted (study 2016-010). The assays evaluated HLA-SAB, C1q-SAB and CDC-CXM as well as a cell-based functional assay using rituximab. In this study, it was shown that the Fc-fragment is still physically attached to the scIgG molecule under physiological conditions and it is not lost upon heat-inactivation which is a commonly used method to inactivate IgM in different assays. Furthermore, it was shown that the HLA-SAB assay, which is based on an Fc-specific detection antibody, cannot discriminate between intact IgG and scIgG and that even small amounts of scIgG can give significant MFI levels in this assay. In contrast, the C1q-SAB assay is not based on an Fc-specific detection antibody and instead recognizes antibodies with C1q complement fixing capacity. ScIgG does not have the capacity to fix C1q in this assay. The CDC capacity of scIgG was evaluated in the cell-based CDC-CXM assay used at the transplant centres and was found to have reduced cytotoxic properties but was not negative when scIgG was present in high concentrations. Another cell-based CDC assay was utilized (based on rituximab) and rituximab as a scIgG molecule had lost its cytotoxic properties.

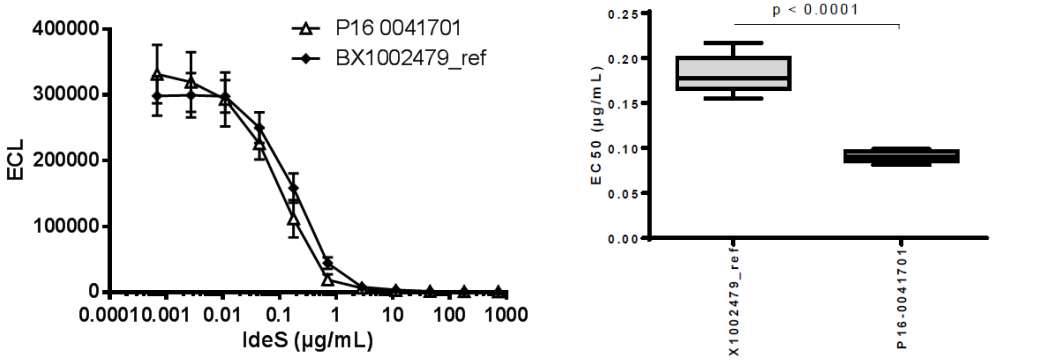
The conclusion from these studies is that scIgG has impaired Fc-mediated effector functions, but may not be completely inactive when present in high concentrations. Thus, dosing with imlifidase should aim at generating the end products ($F(ab')_2$ and Fc) to ensure that all Fc-mediated effector functions are neutralized.

***Potency and comparability exercise between manufacturing Processes 1 and 2***

Potency on purified IgG1, human serum and cell-based functional assays (study 2017-055)

The majority of the primary PD studies conducted during the non-clinical development of imlifidase were performed with material originating from Process 1. A series of bridging studies were conducted with material from Process 2. Data from experiments with purified IgG1 (Humira) indicate that there is a about twofold potency difference between Process 1 and 2 material (**Figure 2**).

**Figure 2 Potency on imlifidase cleavage of a human monoclonal IgG1 antibody (Humira)**



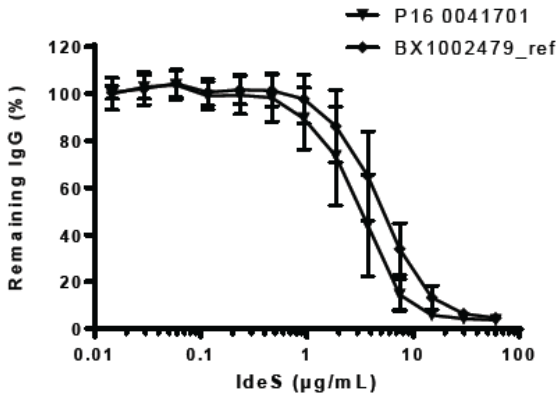

| BX1002479_ref | P16-0041701 |
|---|---|
| % | % |
| 100 | 201 |

*Sigmoidal dose-response (variable slope), no constrains*

Mean ECL plotted for each experiment (duplicate samples) and error bars show SD of six experiments (left). $EC_{50}$ values plotted for the two batches in the IgG1 potency assay (n = 6). Box-plot with min and max are shown for each batch. Statistical comparison using unpaired t-test (right).

This potency was reduced when human serum was used for potency determination (**Figure 3**).

**Figure 3 Potency in human serum**



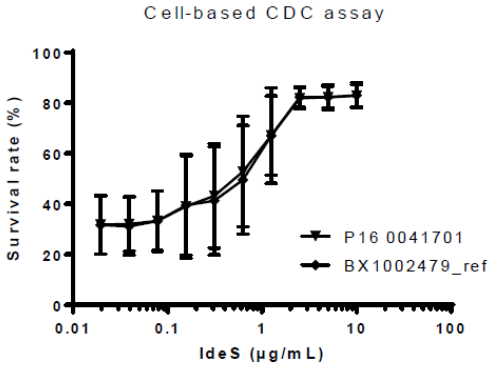

| BX1002479_ref | P16-0041701 |
|---|---|
| % | % |
| 100 | 159 |

*Sigmoidal dose-response (variable slope), no constrains*

Potency in human serum, mean of all subjects: Mean remaining IgG plotted for the two batches using human sera in the serum potency assay. BX1002479_ref$EC_{50}$ (BX1002479_ref): 4.9 µg/mL, $EC_{50}$ (P16-0041701): 3.1 µg/mL. Potency in serum was also calculated in relation to a reference protein i.e. $EC_{50}$ of the reference was set to 100% and the comparing batch $EC_{50}$ value was given a percent value. The potency in serum for the two batches showed 159% potency for Process 2 compared to the reference batch of Process 1 (lower table).

In performed cell-based functional assays the potency differences could not be observed anymore (**Figure 4**).

**Figure 4 Functional potency in human serum**




N = 12 (9 individual + 3 pools)

| BX1002479_ref | P16-0041701 |
|---|---|
| % | % |
| 100 | 110 |

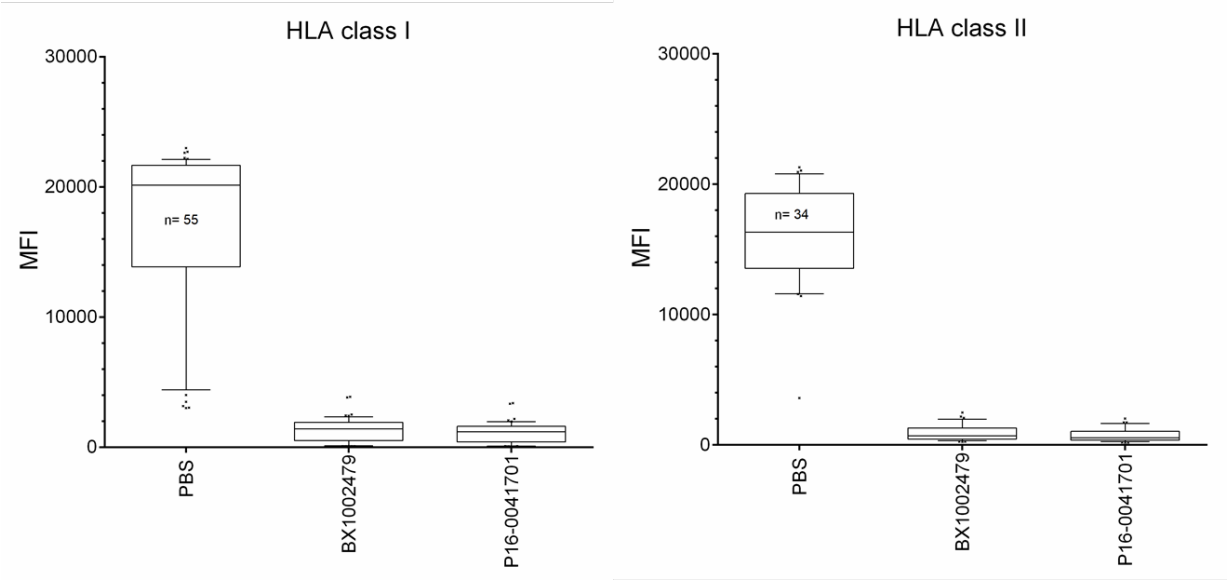
*Sigmoidal dose-response (variable slope), no constrains*

Functional potency assay, mean of all subjects: Mean survival rate plotted for the two batches using human sera and rituximab in a CDC assay (error bars represent SD). Potency was also calculated by assigning the $EC_{50}$ of the reference batch to 100%. The functional potency in serum for the two batches showed 110% potency for P16-0041701 compared to the reference batch BX1002479_ref (lower table).

Effect on HLA (study 2018-047R)

There were no difference in remaining HLA antibodies in sera after treatment with imlifidase from Process 1 and Process 2 as determined in a single antigen bead assay (HLA-SAB, class I and class II, **Figure 5**).

**Figure 5 Box plots of HLA antibodies after treatment with two different imlifidase batches. Example of effect in a highly sensitized patient. Vehicle (PBS), Process 1 (BX1002479), and Process 2 (P16-0041701) batches.**




The number (n) of HLAs having a pre-dose MFI above 3000 is provided in the graph.

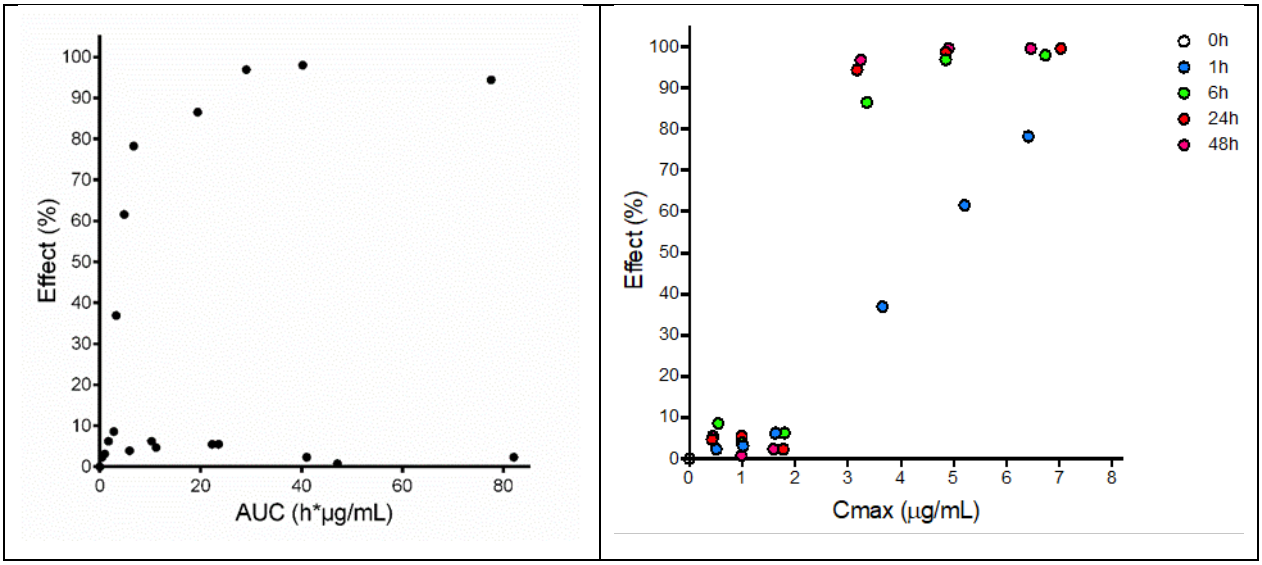
**Effect on IgG: $C_{max}$ vs AUC (2018-010R)**

A human serum pool (N=100) was subjected to imlifidase treatment using a concentration range from 0.5-8 µg/mL and samples were incubated for 1–48 hours. The concentration of imlifidase in the samples was measured and the results show that the imlifidase concentrations were not affected by the duration of the incubation. In addition, there were no statistically significant differences regarding measured imlifidase concentrations between the 2 imlifidase batches.

The IgG level in the serum samples was analysed using the PD assay (effect in serum). This assay reports the sum of IgG and scIgG present in a sample.

Comparing the concentration data with the effect data shows a high correlation between imlifidase $C_{max}$ concentration and effect (**Figure 6**).

**Figure 6 Efficacy of Process 2 imlifidase vs AUC and $C_{max}$. Remaining IgG plotted vs AUC and $C_{max}$ after 1, 6, 24, and 48 hours for imlifidase (P16-0041701) in a human serum pool (N = 100). In the AUC graph, efficacy has been plotted against the AUC generated using all investigated imlifidase concentrations (0.5-8 µg/mL) and the different incubation times (1-48 hours). For easier visualization of the low AUC area, a cut-off for the x-axis was set at 85 h•µg/mL, since higher AUC was only reached when $C_{max}$ was ≥ 4 µg/mL and resulted in full effect.**




In the AUC graph, efficacy has been plotted against the AUC generated using all investigated imlifidase concentrations (0.5-8 µg/mL) and the different incubation times (1-48 hours). For easier visualization of the low AUC area, a cut-off for the x-axis was set at 85 h•µg/mL, since higher AUC was only reached when $C_{max}$ was ≥ 4 µg/mL and resulted in full effect.

Extended cleaving (study 2018-073R)

To address extended cleaving with Process 1 and Process 2 material, IVIg was used as substrate, including all possible substrates for imlifidase as well as naturally occurring ADAs and incubated with a wide range of imlifidase concentrations for an extended period (24-hour treatment). The data show that no additional fragments were generated after prolonged exposure even at very high concentrations (240 µg/mL imlifidase) and that the change in manufacturing has not altered the cleavage pattern.

***In vivo* PD data**

*In vivo* primary PD data were collected from toxicity studies in rabbits and dogs. Despite incomplete IgG cleavage in dogs, the data suggest that the degradation of IgG in both species is very rapid as

most IgG was cleaved in less than 5 minutes, and that the cleavage products generated from imlifidase activity remain in circulation for an extended period of time. The serum concentration vs. time profiles indicate that the levels of both $F(ab')_2$ fragments and Fc-fragments reaches baseline levels between 24 and 48 hours after imlifidase administration, reflecting a controlled elimination of the products generated after imlifidase treatment in both species.

A single high dose, 72-hour study, using 20 mg/kg imlifidase from either Process 1 or Process 2 has been conducted in rabbits (Study 2018-042R). The PD data showed that all animals responded with a profound reduction in IgG levels and were below detection level already at the first sample collection point (5 min) using both materials.

## *Secondary pharmacodynamics*

Secondary PD *in vitro* studies indicated that imlifidase does not cleave the Ig isotypes IgA, IgE, IgD or IgM (Study 2012-009). It was also demonstrated that the IgM-type of BCR present on human lymphoma cell lines are not affected by imlifidase. In addition, it was concluded that imlifidase is able to cleave the IgG-type of BCR present on human lymphoma cell lines with comparable efficacy as to cleavage of IgG present in serum, but this had no impact on proliferation of the lymphoma cell lines. No relevant impact of imlifidase on human granulocytes nor on fibrinogen could be observed.

No further studies to demonstrate off-target cleavage of other peptides/proteins by imlifidase has been provided by the applicant. However, published data are available indicating that IdeS has a high substrate specificity and specifically cleaves IgGs. It has been demonstrated that proteins or synthetic peptides containing sequences such as the P4-P1 segment in the IgG cleavage site, or long peptides resembling the IgG hinge, were not hydrolysed by IdeS. This is likely due to a second binding site interacting with the Fc part of IgG (Vincents et al, 2004, Wenig et al, 2004). As sufficient published data of the specificity of IgG cleavage of IdeS and the underlying mechanism are available, no further studies have been performed with imlifidase.

## *Safety pharmacology*

Respiratory and cardiovascular safety was assessed as part of repeat dose toxicity studies in dogs. No noteworthy findings were reported.

Due to lack of an adequate pharmacological effect in rats, the CNS safety of imlifidase was not assessed. No data on brain distribution of imlifidase are available due to the difficulty of determining distribution of radioactive labelled proteins, which is in line with guideline ICH S6 (R1). However, it is considered unlikely that imlifidase crosses the blood brain barrier (BBB) because of the molecular weight of imlifidase (approximately 35 000 Da) and of its hydrophilicity (>500 exposed hydrogens), the cut-off for lipid-mediated free diffusion across the BBB being <400 Da and <8 hydrogen bonds formed with water (Pardridge, 2012). Active transport of imlifidase is also considered highly unlikely due to the large size of the molecule. Imlifidase crossing through the BBB is also considered unlikely based on the observed low volume of distribution in humans (034-0.055 L/kg (min:max) initially, 0.14 L/kg in the elimination phase ($V_z$) and 0.12 L/kg at steady state ($V_{ss}$)). There were no signs of CNS toxicities during standard observations in rabbits. In dog toxicity studies, minimal to slight infiltration of inflammatory cells in the meninges and choroid plexus of the brain and spinal cord, focal slight to moderate acute perineural inflammation in the spinal cord, sciatic nerve and both optic nerves, including necrosis were observed. These findings are probably immune system related and not a direct effect of imlifidase on the nervous system.

### *Pharmacodynamic drug interactions*

Pharmacodynamic drug interactions were investigated in terms of cleavage of common IgG antibody-based therapeutics. Relevant cleavage has been detected at clinically relevant doses. Eight monoclonal antibodies/fusion proteins were tested and 6 were found to be fully cleaved at clinically relevant doses of imlifidase: adalimumab (Humira®), alemtuzumab (Campath®), basiliximab (Simulect®), denosumab (Xgeva®), etanercept (Enbrel®) and rituximab (Mabthera®). All antibodies and fusion proteins, except for ATGAM, were cleaved by imlifidase, even though the concentration of imlifidase needed to provide a complete cleavage varied, from 0.1 µg/mL to >200 µg/mL, rabbit ATG and betalacept being the most sensitive (fully cleaved at 1/10$^{th}$ clinically relevant dose), and eculizumab being the most resistant.

Eculizumab (Soliris®) was found to be resistant to imlifidase degradation and only processed into scIgG at clinically relevant doses.

## 2.3.3. Pharmacokinetics

No formal PK studies have been performed with imlifidase and PK data of imlifidase were derived from toxicity studies performed in rabbits and dogs. As imlifidase is a protein in line with ICH S6 (R1) no tissue distribution, metabolism and excretion studies have been conducted. Imlifidase was detected in rabbit and dog serum by validated ELISA and ECL methods. All PK calculations were performed using a non-compartmental analysis except for one tolerance study in female rabbits where a 2-compartmental analysis was used.

**Rabbit**

The PK of imlifidase was initially evaluated in the rabbit in association with a preliminary toxicity study investigating doses of 2 or 20 mg/kg of Process 1 imlifidase. The PK profile of imlifidase was evaluated from samples collected after administration on Day 1 and Day 22. Following $C_{max}$, the serum concentration of imlifidase declined rapidly, exhibiting a rapid distribution phase and a slow elimination phase.

In the dose range finding studies, Process 1 imlifidase was administered daily for 10 and 7 days, respectively, at 4 or 12 mg/kg. No accumulation of imlifidase between Day 1, 3, 5 and 7 could be detected. The concentration data obtained allowed for a reliable estimation of the PK parameters of imlifidase for 24 hours after the first dose. The volume of the central compartment (V) of the 2-compartment model was approximately 4% of the body volume, i.e. similar to the plasma volume. The mean value of volume of distribution in steady state ($V_{ss}$) was 0.059 L/kg, i.e. approximately 6% of the body weight was reached by imlifidase.

A characterization of the PK of imlifidase was furthermore conducted during the pivotal repeat dose toxicity study in rabbit where the Process 1 material was administered at 0.2, 2 and 20 mg/kg on 4 occasions, 1 week apart. The PK profile was evaluated from samples collected after the first and last dosing occasions. All animals dosed with imlifidase were exposed systemically to the compound during the study. The shape of the serum concentration time curve of imlifidase indicated a multi-phase elimination profile. There was no difference in $C_{max}$ between genders. The female animals had somewhat lower average clearance compared to the male animals on Day 1. No difference in distribution volume could be seen between genders. The mean exposures to imlifidase increased essentially in a dose proportional way after both first and last dosing occasions (**Table 2**).

After 2 and 3 once weekly doses (Days 8 and 15), imlifidase serum concentrations (1 hour after dosing) were comparable to the first dose, in all 3 dose groups. After receiving the 4$^{th}$ dose on Day 22, the animals in the lowest dose group (0.2 mg/kg) had unquantifiable serum concentrations and this is most probably due to high levels of ADA developed. All animals in the 2 and 20 mg/kg groups had

detectable imlifidase concentrations on Day 22. Exposure could not be calculated on Day 22 for 1 animal in the 2 mg/kg group, and for 1 animal in the 20 mg/kg group. Further, two animals in the 2 mg/kg group had much lower exposure on Day 22 compared to Day 1. For the remaining animals in the 2 and 20 mg/kg groups (n=12), the total imlifidase exposure increased in average 4-fold on Day 22 compared to Day 1 (**Table 2**). The clearance decreased after repeat dosing whereas the distribution volume of imlifidase increased.

**Table 2 PK parameters after first and last dose**

| **Dose (mg/kg)** | **Day** | **N[a]** | **Cmax (µg/mL)** | **AUC (h×µg/mL)** | **t1/2 (h)** | **CL (L/h/kg)** | **Vz (L/kg)** | **Vss (L/kg)** |
|---|---|---|---|---|---|---|---|---|
| 0.2 | 1 | 6/6 | 4.6 | 5.6 | 0.9 | 0.036 | 0.046 | 0.044 |
| | 22 | 6/6 | <LOQ | N/A | N/A | N/A | N/A | N/A |
| 2 | 1 | 6/6 | 80 | 69 | 1.2 | 0.031 | 0.052 | 0.035 |
| | 22 | 5/6 | 17 | 180 | 9.9 | 0.53 | 0.41 | 0.37 |
| 20 | 1 | 10/10 | 460 | 670 | 4.4 | 0.032 | 0.19 | 0.075 |
| | 22 | 8/10[b] | 430[c] | 2500 | 16 | 0.011 | 0.26 | 0.19 |

<LOQ: Below the Limit of Quantification
N/A Not applicable
[a]Number of animals included in parameter calculation/number of animals in treatment group
[b]One animal died in connection to 3rd dosing.
[c]Calculated on data from 9 animals

***Comparison of kinetics of Process 1 and 2 imlifidase material in rabbit***

A comparison of the exposures obtained on Day 1 in the 4-week rabbit studies with the two materials shows consistent figures on $C_{max}$ and AUC between the studies (**Table 3**).

**Table 3 Comparison of mean exposure parameters obtained on Day 1 in the 4-week rabbit studies with Process 1 (Study 2012-011) and Process 2 (Study 2018-075R) materials**

| | Dose (mg/kg) | Gender | $C_{max}$ (µg/mL) | AUC (hr•µg/mL) | AUCDose (hr•µg/mL)/ (mg/kg) |
|---|---|---|---|---|---|
| Frozen, Process 1 | 0.2 | Female | 4.50 | 6.29 | 31.5 |
| | | Male | 4.64 | 4.99 | 24.9 |
| | 2 | Female | 93.5 | 80.5 | 40.3 |
| | | Male | 65.7 | 56.8 | 28.4 |
| | 20 | Female | 483 | 811 | 40.6 |
| | | Male | 435 | 525 | 26.3 |
| Lyophilized, Process 2 | 0.2 | Female | 5.50 | 3.94 | 19.7 |
| | | Male | 5.98 | 4.03 | 20.2 |
| | 2 | Female | 50.6 | 44.7 | 22.4 |
| | | Male | 55.5 | 41.4 | 20.7 |
| | 12 | Female | 342 | 387 | 32.2 |
| | | Male | 332 | 361 | 30.1 |

In order to evaluate potential PK differences between Process 1 and Process 2 imlifidase, PK after the first dose from all rabbits dosed with Process 1 imlifidase was compared to first dose PK from all rabbits dosed with Process 2 imlifidase. Data collected from six studies were included in the comparison and consisted of all together 48 concentration time profiles from Process 1 in the dose range of 0.2 to 20 mg/kg and 34 concentration time profiles from Process 2 in the dose range of 4 to 20 mg/kg.

Serum concentration versus time data were analysed by non-compartmental analysis (NCA) in Phoenix® WinNonlin® 64, version 8.0, build 8.0.0.3176 (Certara, USA). The AUC method used was the 'linear up log down', and the plasma (or serum) model (200-202). For each of the PK parameters $C_0$, $C_{max}$, $AUC_{0-24h}$, and $AUC_{inf}$ a plot of the log-transformed data against the log-transformed dose were constructed including the line from the linear regression. Geometric mean ratios were calculated for $C_0$, $C_{max}$, $AUC_{last}$, $AUC_{0-24h}$ and $AUC_{inf}$. Dose proportionality was observed for both $C_{max}$ and AUC for both imlifidase materials combined.

The 90% CI for the relative difference in geometric means between Process 1 and Process 2 imlifidase for all of the investigated parameters except $AUC_{inf}$ (90% CI 0.793, 1.017) were within the bioequivalence limits of 0.80–1.25 suggesting equivalent serum disposition of the 2 materials. Since there is a difference in the amount of oxidized isomer present in Process 1 compared to the Process 2 imlifidase, the applicant concluded that the equivalent PK behaviour of the two materials suggest a similar PK behaviour of imlifidase and its oxidized isomer.

**Toxicokinetics in Pivotal Embryo-foetal Development Study in Rabbits (Study 2017-181)**

Serum concentrations generally exhibited moderate variability at each time point across dose groups and days. The time course of imlifidase concentration across the 24-hour sample period showed a postdose bi-phasic decline after single dosing (GDs 6 and 13) and a tri-phasic decline following repeat dosing (GDs 12 and 19), depicted by a more rapid initial postdose decline in imlifidase concentrations up to 1 hour postdose compared to after a single dose. This may be indicative of enhanced clearance due to positive ADA response after multiple dosing.

**Dog**

The PK of imlifidase was initially evaluated in the preliminary toxicity investigating doses of 2 or 20 mg/kg in dogs. Serum samples were collected to allow for the characterization of the complete serum concentration time profile after Day 1 administration and samples from only a few time points were collected after repeated dosing.

A characterization of the PK of imlifidase was further conducted during the pivotal repeat-dose toxicity study in dogs where Process 1 imlifidase was administered at 0.2, 2 and 20 mg/kg on two occasions, one week apart. The PK profile was evaluated from samples collected after dosing. All animals dosed with imlifidase were exposed systemically to the compound during the study. The shape of the serum concentration time curve of imlifidase indicated a multi-phase elimination profile.

There was no difference in exposure ($C_{max}$ and AUC) between genders. The mean exposures to imlifidase increased essentially in a dose proportional way on both dosing occasions (**Table 4**)**.**

**Table 4 Mean PK parameters in male and female dogs combined after first and last Dose.**

| **Dose** (mg/kg) | **Day** | **N** | **$C_{max}$** (µg/mL) | **AUC** (h×µg/mL) | **$t_{1/2}$** (h) | **CL** (L/h/kg) | **$V_z$** (L/kg) | **$V_{ss}$** (L/kg) |
|---|---|---|---|---|---|---|---|---|
| 0.2 | 1 | 6 | 3.3 | 15 | 19 | 0.015 | 0.15 | 0.12 |
| | 8 | | 3.7 | 26 | 22 | 0.012 | 0.14 | 0.12 |
| 2 | 1 | 6 | 34 | 180 | 24 | 0.012 | 0.41 | 0.18 |
| | 8 | | 33 | 290 | 47 | 0.0081 | 0.37 | 0.24 |
| 20 | 1 | 10 | 380 | 2600 | 13 | 0.0082 | 0.16 | 0.084 |
| | 8 | | 310 | 1100 | 21 | 0.022 | 0.64 | 0.32 |

Overall, there was no major difference in exposure after 2 doses compared to one at any dose level tested. For the two lower dose levels (0.2 and 2 mg/kg), 11 out of 12 animals showed higher AUC on Day 8 compared to Day 1 (less than 2-fold increase in mean exposure). In the high dose group (20 mg/kg), the opposite was observed, i.e. 9 out of 10 animals showed lower exposure after the last dose (Day 8) compared to first dose (Day 1), while one male showed higher exposure (1.2-fold). It is assumed that the higher clearance at Day 8 is due to the presence of drug clearing ADA. One dog presented ADA at Day 8. However, as the detection reagent used in the PD and ADA assays could not detect all dog IgG subclasses, it is thus possible that the ADA response was misinterpreted. In a supplementary investigation, the pre-dose (i.e. Day 1 and Day 8) samples from all animals in the pivotal study were re-evaluated for presence of ADA using an imlifidase specific bridging assay. Three animals had detectable ADA against imlifidase prior to the last dose (Day 8), and this response increased further after the last dose.

The applicant stated that the exposure in high dose animals was 64- and 12-fold the clinical $C_{max}$ and AUC, respectively.

## 2.3.4. Toxicology

The toxicology programme of imlifidase was conducted to support a single-dose intravenous administration for pre-transplant treatment of patients that are sensitized to donor tissue. Since imlifidase was shown to be a potent and specific protease for human and rabbit IgGs, rabbits were selected as the primary species for toxicity testing.

The toxicological programme (**Table 5**) consisted of single and repeat-dose toxicity studies, reproductive and developmental studies one pilot and one GLP embryo-foetal development (EFD) study. In addition, non-GLP follow-up studies were performed on findings that occurred in the repeated-dose toxicity studies. Toxicological studies were mostly conducted with imlifidase from process 1 (frozen solution). The pilot and GLP EFD studies as well as a bridging GLP repeat-dose toxicology study in rabbits were conducted with imlifidase proposed for commercial use (process 2, lyophilized drug product).

**Table 5 Toxicology studies conducted with imlifidase**

| Study type and duration | Route of administration | Species | Study No. |
|---|---|---|---|
| *Single dose toxicity* | | | |
| Single dose toxicity | IV | Rabbit | 2012-035 |
| Single dose toxicity | IV | Rabbit | 2018-042R |
| Single dose toxicity | IV | Dog[a] | 2012-007 |
| *Repeated dose toxicity* | | | |
| 7 Days (daily dosing) | IV | Rabbit | 2016-062 |
| 10 Days (daily dosing) | IV | Rabbit | 2016-003 |
| 4 Weeks (weekly/every 10 days dosing) | IV | Rabbit | 2012-006 |
| 4 Weeks (weekly dosing) | IV | Rabbit | 2012-035 |
| 4 Weeks (Pivotal, weekly dosing), GLP | IV | Rabbit | 2012-011 |
| 4 Weeks (Pivotal, weekly dosing), GLP* | IV | Rabbit | 2018-075R |
| 2 Weeks (Pivotal, weekly dosing), GLP | IV | Dog | 2012-012 |
| 3 Weeks (weekly dosing) | IV | Dog | 2012-007 |
| *Reproductive and Development Toxicity* | | | |
| Preliminary study | IV | Rabbit | 2017-004R |
| Pivotal study, GLP* | IV | Rabbit | 2017-181R |

[a] One single animal

*Studies conducted with process 2 material

## *Single dose toxicity*

Single doses of imlifidase were only administered and evaluated as part of two non-GLP repeated dose studies; one study in rabbits and one study in a dog. In addition, a bridging study comparing the effects of imlifidase manufactured via Process 1 and Process 2 was conducted in rabbits.

**Table 6 Overview single dose toxicity study**

| Species/ Strain | Method of Administration (Vehicle/Formulation) | Doses (mg/kg) | Gender and No. per Group | Observed Max. Non-Lethal Dose (mg/kg) | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|
| NZW Rabbit | IV (PBS / solution for injection) | 0, 20 | 5M+5F | 20 | Histopathology: Lung, increased alveolar histiocytosis, presence of perivascular/alveolar macrophage aggregates and perivascular | 2018-042R |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | heterophils compared to controls. | |
| NZW Rabbit | IV (PBS / solution for injection) | 0[a], 20 | 4M+4F 10M+10F (5M+5F in imlifidase group were terminated on Day 4 and 5M+5F were terminated on Day 24) | 20 | Macroscopic pathology:<br>3 days after dosing; red discolouration of the lungs in N=3/10 animals treated with 20 mg/kg, correlating with congestion in vessels and capillaries.<br>After 3 weeks of recovery red discoloration (20 mg/kg, N=2/10).<br>Histopathology:<br>Lung, 3 days after dosing; increased alveolar macrophages, in all animals, subacute inflammation (N=6/8, control; N=10/10, 20 mg/kg), vascular congestion (N=3/8, control; N=4/10, 20 mg/kg). The grading was higher in imlifidase treated animals than in controls.<br>Moderate focal alveolar oedema mainly in 1 lung lobe in 1 animal at 20 mg/kg.<br>Lung, after 3 weeks recovery; increased alveolar macrophages (N=10/10), subacute inflammation (N=8/10), vascular congestion (N=4/10), minimal haemorrhage (N=3/10), and alveolar oedema (N=2/10).<br>The gradings were higher versus 3 days after dosing. | 2012-035 |
| Beagle dogs HsdRcc:DOBE | IV (0.9% saline solution) | 2 | 1F[b] | 2 | None | 2012-007 |

F=female, IV=intravenous, M=male, NZW=New Zealand white, PBS=phosphate buffered saline
[a]Control animals received once weekly dosing of vehicle for 4 weeks
[b]The animal was terminated 29 days after dosing (Day 30)

## *Repeat-dose toxicity*

**Table 7 Overview of non-GLP repeat-dose toxicity studies**

| Species/ Strain | Method of Admin. (Vehicle / Formulation) | Duration of dosing | Doses (mg/kg) | Gender and No. per Group | NOAEL[a] (mg/kg) | Noteworthy Findings | Study Number |
|---|---|---|---|---|---|---|---|
| NZW Rabbits | IV (PBS / solution for injection) | 7 days | 0, 4, 12; once daily | 4F | Not formally established | Macroscopic pathology: Slightly enlarged spleen in N=2/4 at 12 mg/kg | 2016-062 |
| NZW Rabbits | IV (PBS / solution for injection) | 10 days | 0<br>4<br>12; once daily | 3F<br>4F<br>4F | Not formally established | Mortality: 1F at 12 mg/kg died after the 8th dose. Necropsy showed: hypostasis of the left ear; prominent white pulp of the spleen; hyperaemic oviducts; hypostasis of the left lung; inflamed parotid and submandibular glands; and petechiae of the thymus.<br>Clinical signs:<br>4 mg/kg: cramp after 8 doses (N=1/4) and 10 doses (N=3/4).<br>12 mg/kg: elevated pulse after dose 10 (N=2/3).<br>Macroscopic pathology:<br>Grainy surface of the spleen and prominent white pulp in N=1/4 at 4 mg/kg;, prominent white pulp of the spleen in N=1/4 at 12 mg/kg;<br>Diffuse hyperaemia of the medulla of the kidneys in N=3/4 at 4 mg/kg and N=1/3 at 12 mg/kg;<br>Hyperaemic uterus in N=1/4 at 4 mg/kg and N=1/4 at 12 mg/kg;<br>Hyperaemic oviducts in N=1/4 at 4 mg/kg; | 2016-003 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | multiple black spots, possibly bleedings, in the ovaries in N=2/3 at 12 mg/kg.<br>Dilated right ventricle (with thin wall) of the heart was observed in one Group 2 and one Group 3 animal. | |
| NZW Rabbits | IV (0.9% saline solution) | 4 weeks | 2, 20; 4 doses, once weekly, or 3 doses, every 10 day | 1M+1F | Not formally established | None | 2012-006 |
| NZW Rabbits | IV (PBS / solution for injection) | 4 weeks | 0, 20; 4 doses, once weekly | 4M+4F | Not formally established | Organs weights: spleen in females statistically significantly enlarged. Same tendency seen in males.<br>Macroscopic pathology: Red discolouration of the lungs, correlating with congestion in vessels and capillaries.<br>Histopathology: Slight to moderately increased alveolar macrophages in the lungs, subacute inflammation, characterised by periarterial and interstitial heterophilic granulocytes and lymphoid cells. This happened also in the control group.<br>Minimal to moderate, focal and multifocal, vascular congestion in several imlifidase treated animals (N=6/8). This happened also in the control group (N=3/8). | 2012-035 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | In summary, same pattern of microscopic findings seen in control group, but at lower gradings.<br>Slight focal alveolar oedema mainly in 1 lung lobe in 1 imlifidase treated animal. | |
| Beagle HsdRcc:DOBE Dogs | IV (0.9% saline solution) | 3 weeks | 2, 20; Once weekly | 1F; and 1M+1F | Not formally established | No noteworthy findings after dose 1 and 2.<br>The 3rd dose induced immune-mediated anaphylactic shock in 1 dog at each dose, thus further administration was stopped. | 2012-007 |

[a]No Observed Adverse Effect Level

**4-week Repeat-Dose Intravenous Toxicity Studies in Rabbits - GLP Studies**

**Study 2012-011 – Process 1 material**

The study design and major findings from the pivotal repeat-dose toxicity study in rabbits (study no. 2012-011) are provided in **Table 8**. At the end of the recovery period, the females treated with 20 mg/kg had recovered whereas recovery was still taking place in the male recovery animal treated with 20 mg/kg. In two of three females treated with 20 mg/kg imlifidase a treatment wide spread peri/-arteritis was found. This was considered to be a treatment-related change.

No test item related changes were seen on the body weight gain, food consumption, ophthalmoscopic examinations, and urinanalysis.

**Table 8 Intravenous Repeat Dose Toxicity Study in Rabbits**

| Study type/<br>Study ID / GLP | Species;<br>Number<br>Female/ group | Route & dose (mg/kg/day) | Dosing period | Major findings | NOAEL (mg/kg/day) |
|---|---|---|---|---|---|
| Study No.:<br>2012-011<br><br>Toxicokinetic<br><br>GLP | Rabbit/<br>NZW<br><br>6/group<br><br>recovery group 4/group (low and high dose) | 0, 0.2, 2 and 20<br><br>intra-venously<br><br>† Day 25<br><br>† Recovery on Day 29 | Day 1, 8, 15 and 22 | All dose groups:<br>Slight to severe erythema<br><br>≥0.2 mg/kg/d:<br>↑ spleen weight,<br>↑ alpha 1 and beta globulins<br>↓gamma globulins<br><br>≥2 mg/kg/d:<br>↑ alveolar macrophages,<br>↑ fibrinogen level | NOAEL:<br>2 |

| Study type/ Study ID / GLP | Species; Number Female/ group | Route & dose (mg/kg/day) | Dosing period | Major findings | NOAEL (mg/kg/day) |
|---|---|---|---|---|---|
| | | | | 20 mg/kg/d: minimal to moderate peri/-arteritis | |

**Study 2018-075R – Process 2 material**

Imlifidase was administered intravenously once weekly for 4 consecutive weeks to groups of 3 New Zealand White rabbits/sex/group at doses of 0 (saline solution), 0.2, 2 and 12 mg/kg. An additional 3 animals/sex of the control and high dose groups were treated similarly but allowed a 4-week recovery period prior to sacrifice. Based on earlier observations of very significant titres of ADAs with the 4 once weekly regimen, an additional group of 6 animals/sex was intravenously dosed with 2 mg/kg once weekly for 2 consecutive weeks of which three animals/sex were sacrificed on Day 11 while the other three/sex were allowed a 4-week recovery period prior to sacrifice. Systemic exposure evaluation was performed on the same animals that were used for toxicity evaluation. In addition, animals were subjected to blood sampling for PD (IgG serum levels) and ADA determinations. None of the regimens produced any relevant in-life observations.

In animals receiving 4 administrations, there were treatment-related but not dose-related effects on myocardium (minimal to moderate inflammatory cell infiltration and minimal to slight myocardial cell degeneration) of the right ventricle at all dose levels investigated (0.2-12 mg/kg) in the 4 once weekly treatment regimen. No heart findings were observed after a 4-week recovery period and no similar heart findings were observed when rabbits were subjected to 2 once weekly injections of 2.0 mg/kg doses of the Process 2 material. Thus, the 2.0 mg/kg dose was established as the NOAEL for imlifidase administered as 2 once weekly IV injections. A supplementary analysis of heart slides from rabbits treated with Process 1 imlifidase material in Study 2012-011 (Study 2019-046R) was performed and showed that the same changes (minimal to slight in severity grading) were present also in animals treated with the Process 1 material, with seemingly higher incidence of the changes at the two higher dose levels (2.0 and 20 mg/kg).

Other target organs identified in study 2018-075R with imlifidase were the spleen and the lung. The spleen changes in high dose animals consisted of increased organ weight and cellularity in the white pulp. Lower dose animals and animals administered 2 once weekly doses of 2 mg/kg had a tendency to increased organ weight but no histological change. The spleen changes were not observed in recovery animals and were not considered adverse. The only treatment-related lung finding with the Process 2 material was an exacerbation (higher severity grading) of perivascular inflammatory cell infiltration, which was observed in essentially all animals including controls and recovery. The change was graded slight in severity and was not considered adverse. Alveolar histiocytosis was also observed in the study with the Process 2 material but there was no higher incidence in imlifidase administered animals than in controls.

**2-week Repeat-Dose Intravenous Toxicity Study in Dogs - GLP Study**

The study design and major findings of the pivotal toxicity study in dogs (study no. 2012-012) conducted with process 1 material are provided in **Table 9**.

**Table 9 Intravenous Repeat-Dose Toxicity Study in Dogs**

| Study type/ Study ID / GLP | Species; Number Female/ group | Route & dose (mg/kg/day) | Dosing period | Major findings | NOAEL (mg/kg/day) |
|---|---|---|---|---|---|
| Study No.: (2012-012)<br><br>Toxicokinetic<br><br>GLP | HsdRcc:DOBE beagle dogs<br><br>6/group<br><br>recovery group: 4/group (low and high dose) | 0, 0.2, 2 and 20<br><br>intra-venously<br><br>† Day 11<br>† recovery Day 29 | Day 1 and 8 | All dose groups:<br><br>20 mg/kg/d:<br>↑ body temperature ♀, one animal sacrificed moribund (day 10), ↑ tubular basophila and focal interstitial fibrosis in kidney | NOAEL:<br>2 |

No treatment related changes were observed at the body weight, food consumption, skin reactions at the injection sites, electrocardiography (ECG), evaluation of respiration rate, ophthalmoscopy, haematology, urinalysis, urine microscopy and macroscopic examination.

Microscopic findings were observed in kidneys of 4 animals, 3 of them at 20 mg/kg of imlifidase. One animal had to be sacrificed moribund. The unilateral minimal interstitial fibrosis recorded in the mid dose male was considered to be within the common background changes in dogs. No treatment-related renal changes were recorded following a treatment-free period of 29 days. Clinical pathology investigations indicated normal kidney function, both for main study and recovery animals.

Tubular basophilia and focal interstitial fibrosis in the cortex of the kidneys are commonly occurring background changes in laboratory maintained Beagle dogs. However, as the incidence and severity of these changes were increased in high dose dogs as compared to controls, it cannot be excluded that there was a treatment-related exacerbation of these common incidental findings.

In male No 29, sacrificed moribund on day 10 of the study, extensive inflammatory reactions were recorded in several organs. The pathology resembled Beagle pain syndrome and this diagnosis was supported by macroscopic and microscopic examination.

None of the dogs had detectable levels of ADA before the first dosing. The majority of the animals in the main groups did not develop detectable ADA during the course of the study (11 days). In a supplementary investigation (2012-030), using an imlifidase specific bridging assay, it was shown, that at least three of the animals were tested positive for ADA before dosing day 8. By day 18, all recovery animals in Group 4 had developed detectable anti- imlifidase antibodies.

From three dogs that showed kidney findings, two had detectable levels of ADAs prior to the second dosing when measured using a supplementary bridging approach and one animal without kidney findings also had detectable ADAs at the time of second dosing. Immune complex-induced injuries in kidney are generally associated with infiltration of inflammatory cells and fibrosis is a later process developing during the healing/remodelling of tissue. Because the animals did not have performed ADA, and ADA is expected to take almost a week to develop, and considering the PK of imlifidase in dog at 20 mg/kg (t½ of approximately 13 hours), immune complexes are not likely to have been able to form

until the second dosing (Day 8). The animals were sacrificed on Day 11 i.e. 3 days after second dosing and thus it is not likely that immune complex mediated injuries could have presented with interstitial fibrosis within this short time frame. Of note is also that the findings were minimal to slight in two animals and only one animal had a moderate note in the pathology report. In this animal the kidney findings were unilateral. The kidney function has been carefully monitored in the clinical studies (Study No. 15-HMedIdeS-06).

## *Genotoxicity*

Imlifidase is a bacterial enzyme (immunoglobulin G-degrading enzyme of *S. pyogenes*), produced by means of recombinant expression in *E. coli*. No genotoxicity studies have been performed since such studies are not applicable for biotechnology-derived pharmaceuticals, in accordance with ICH Guideline: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals ICH S6 (R1)2.

## *Carcinogenicity*

Imlifidase is intended for single dose use, therefore imlifidase has not been tested for carcinogenicity. This is agreed by CHMP.

## *Reproduction Toxicity*

The reproductive and developmental toxicity of imlifidase was evaluated in an EFD study in rabbits. Significant immunogenicity hindered the formal testing of effect on fertility and early embryonic development; therefore, no fertility studies were performed. Fertility was assessed in repeat-dose toxicity studies in rabbits and dogs performing histological examination of reproductive organs. No pre-/post-natal development studies were performed. No reproductive toxicity testing was performed in the rat, as imlifidase is not fully pharmacologically active (only partial cleavage of the IgG)) in this species.

Doses for the EFD study in the rabbit were selected based on a dose range finding study. The pivotal studies were performed in accordance with GLP.

The dose range finding EFD study was conducted with the drug substance (Process 2) and the pivotal EFD study was conducted with the drug product (Process 2).

**Dose range Embryo-foetal Development Study in Rabbits (Study 2016-0186-R)**

In the non-GLP dose range-finding developmental toxicity study in rabbits, imlifidase was administered intravenously at dose levels of at 4 mg/kg and 12 mg/kg (1.2 mL/kg), either from Gestation Day (GD) 6 to GD 12 or from GD 13 to GD 19. Satellite groups were included to assess the pharmacology of imlifidase (IgG concentration), presence of ADA and exposure evaluation.

No clinical signs were observed during the study. No treatment related changes in BW or BW gain occurred at any dose during pregnancy. No treatment related changes in food or water consumption occurred during the study. All animals were found to be pregnant except 1 animal in the control group, and all of these bore live foetuses. Neither total resorptions nor signs of abortion were seen. There were no deaths following the administration of imlifidase at any dose level.

All rabbits developed an ADA response.

**Pivotal Embryo-foetal Development Study in Rabbits (Study 2017-181)**

Study design and major findings of the GLP EFD study conducted in rabbit is provided in **Table 10**.

**Table 10 Intravenous Embryo-fetal Developmental Toxicity Study in Rabbits**

| Study type/ Study ID / GLP | Species; Number Female/ group | Route & dose(mg/ kg/day) | Dosing period | Major findings | NOAEL (mg/kg/day) |
|---|---|---|---|---|---|
| Doc. No. 2017-181<br><br>Toxicokinetic<br><br>GLP | Rabbit/ NZW<br><br>20/Group<br><br>Satellite Group 3/group | 0, 4 and 12<br><br>intra-venously | Staged dosing: Gestation day 6 to 12 or 13 to 19 | none | maternal toxicity NOAEL: 12<br><br>NOAEL embryo fetal development: 12 |

Daily dosing for more than 8 days in rabbits was associated with hypersensitivity reactions, therefore a staged dosing was selected for the EFD study using 2 cohorts, one with administration during gestation days 6-12 and one during gestation days 13-19 of gestation in order to cover the entire organogenetic period for the species. The compound was well tolerated by pregnant animals at all doses tested, regardless of the period of administration. In presence of proven activity of the test item, namely reduction of IgG in the serum, and exposure for entire period of dosing, there was no indication of teratogenic effect at any of the dose-levels or period of administration tested. All dosed animals developed ADA after repeat dosing. The maternal and foetal NOAEL was established at 12 mg/kg. The applicant conducted no histopathology evaluations of rabbit females.

For the intended indication (single application, non-pregnant), no prenatal and postnatal development study was performed, because transplantation will not be performed during pregnancy and women of child bearing potential should refrain to become pregnant.

## *Local Tolerance*

No stand-alone local tolerance studies were conducted. Local tolerance was assessed as part of a 4 week-weekly dosing study, a stage 7 days daily dosing embryo-fetal development in rabbits and a 2 weeks weekly dosing study in beagle dogs.

In the repeat dose intravenous toxicity study in rabbits, slight to severe erythema were observed at the injections sites in most of the animals in Groups 1-4. As the incidence and severity of the erythema were comparable among the groups treated with the vehicle (Group 1) or imlifidase (Groups 2-4), this finding was considered to be related to the intravenous injection procedure or the vehicle rather than the test item *per se.*

In the repeat dose intravenous toxicity study in dogs, no skin reactions at the injection sites were found in any of the treated animals.

Both studies were done with the imlifidase drug product obtained from Process 1. To also assess the local tolerance of imlifidase drug product manufactured *via* Process 2, a local tolerance assessment was also performed during the GLP embryofetal development study in rabbits. No noteworthy local signs at the injection site were seen in the intravenous embryo-fetal developmental toxicity study in the rabbit.

## *Other toxicity studies*

### Antigenicity

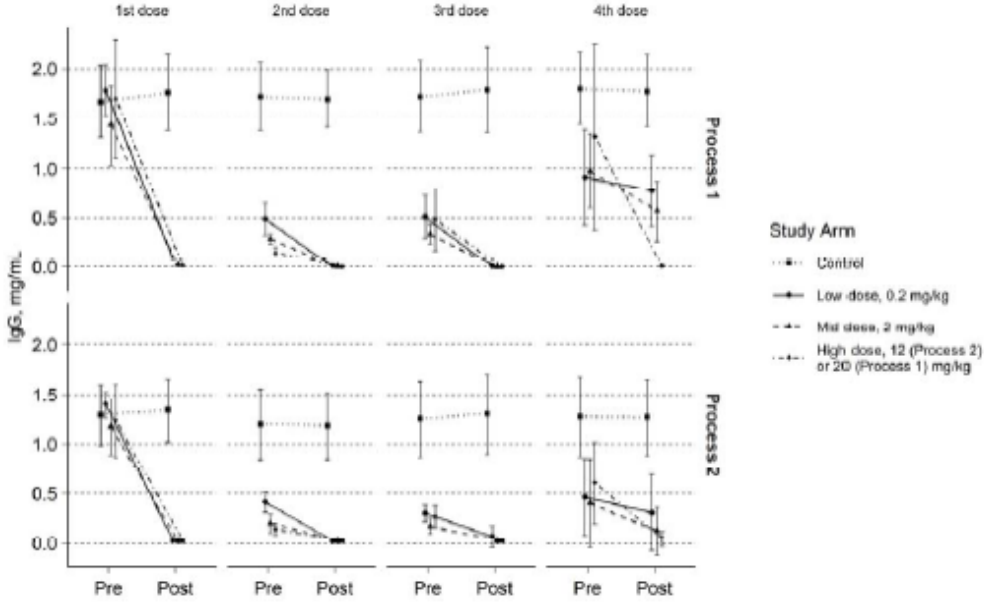
*Anti-drug antibody response in rabbit toxicology*

All rabbits treated with imlifidase, independently of dose, developed detectable levels of ADA. The ADA-response in the rabbit is mainly of the IgM and IgG classes and the time-course of the development of IgM-ADA and IgG-ADA are quite similar. However, the IgG response peaks approximately ten days later than the IgM response. None of the tested rabbits had detectable ADA of the IgA class during the course of the study.

Supplementary investigation to study Study No. 2012-011 (process 1 material) and Study 2018-075R (process 2 material)

A comparison of the IgG serum levels from the two 4-week repeat dose studies in rabbits is presented in **Figure 7**. The results show comparable efficacy of the Process 1 and Process 2 materials.

**Figure 7 Comparison of IgG concentration (ng/mL) obtained in repeat-dose studies with the frozen (Process 1) and lyophilized (Process 2) drug products.**




Data are presented as mean +/-SD

When comparing the ADA titres from the 0.2 and 2.0 mg/kg dose groups from the two studies it can be seen that all animals had significant titres prior to the third dose on Day 15 (**Table 11**). No clear difference between the two materials in their ability to induce ADAs could be observed from these data. It should be noted that ADA in study 2012-011 (Process 1) was not further titrated above 128000.

**Table 11 Comparison of incidence and range of ADA titres at different days in repeated-dose studies in rabbits with the frozen (Process 1) and lyophilized (Process 2) drug products at dose levels of 0.2 and 2.0 mg/kg.**

| Day predose | Dose (mg/kg/week); Drug substance process | | | |
|---|---|---|---|---|
| | 0.2, Process 2 | 0.2, Process 1 | 2.0, Process 2 | 2.0, Process 1 |
| 1 | 0/6 (-) | 0/6 (-) | 0/6 (-) | 0/6 (-) |
| 8 | 2/6 (100-759) | 0/6 (-) | 5/6 (100-280) | 0/6 (-) |
| 15 | 6/6 (206-54254) | 6/6 (8000-32000) | 6/6 (2906-31830) | 6/6 (16000-≥128000*) |
| 22 | 6/6 (15528-562845) | 6/6 (≥128000*) | 6/6 (14380-613545) | 6/6 (≥128000*) |

*ADA was not titrated above 128000

*Anti-drug antibody response in dog toxicology*

In a supplementary analysis (Study No. 2012-033), development of anti-fragment antibodies could not be verified in any of the 12 animals tested from the repeat-dose toxicity study in the dog (Study No. 2012-012). The sensitivity of the assay allowed for detection of approximately 30 ng/ml anti-dog IgG antibodies in a sample, which corresponds to a detection limit of 3 µg/ml anti-fragment antibodies in serum when corrected for the sample dilution factor (100-fold).

The titres of IgG-ADA were measured using a validated assay in all animals before first dosing (pre-1st), before second dosing (pre-2nd), at termination of the main group (day 11) and during the recovery period (day 18, day 25, day 32 and day 37) (supplementary Study No 2012-030). The majority of the dogs in the main groups did not develop detectable ADA during the course of the study. However, using a specific imlifidase bridging assay (ELISA assays to further characterize the ADA response in the dog toxicology study, study 74332), three animals in the highest dose group (20 mg/kg) were tested positive for ADA on day 8, i.e. before the second dosing. The response was mainly of the IgG class. None of the tested animals were tested positive for IgM or IgA ADA. After the second dosing the ADA response further increased in all three animals. After the second dosing, the ADA response further increased in all three animals. In addition, one recovery animal had also detectable ADA levels 72 hours after the second dosing. Except for one animal, none of the animals, including the recovery animals, had any adverse reactions or increase in acute phase protein responses despite the presence of ADA. Another animal developed an ADA response after the first dosing of imlifidase, there is no clear correlation between animals that developed anti-imlifidase antibodies and a clinical adverse reaction. It cannot completely be excluded that the adverse reaction starting 96 hours after first dosing in the dog No 29 is the result of an immune complex mediated hypersensitivity reaction to imlifidase. Two other dogs also developed significant levels of ADA after first dosing, but tolerated even repeat dosing in the presence of ADA.

The aim of the supplementary Study No. 2012-040 was to investigate the level and time-course of serum IgA in all animals in the repeated dose dog study 2012-012. The highest concentrations of IgA, during the course of study, were measured in serum from two dogs of the high dose group. In serum from these dogs, IgA culminated at 24 h after the second imlifidase dose (i.e. Day-9) at 2.95 mg/ml and 2.57 mg/ml. These two dogs showed an elevation in IgA concentration in the serum prior the second dosing of imlifidase indicating an increase between day 4 and 8. When comparing pre-1st dose level of IgA to maximum measured level (i.e. Day-9), one dog showed a four-fold increase in IgA, which is the largest change among the animals. The other dog had a two-fold increase in IgA. The median pre-treatment IgA concentration in the 32 dogs was 0.69 mg/ml, with a range from 0.26 to

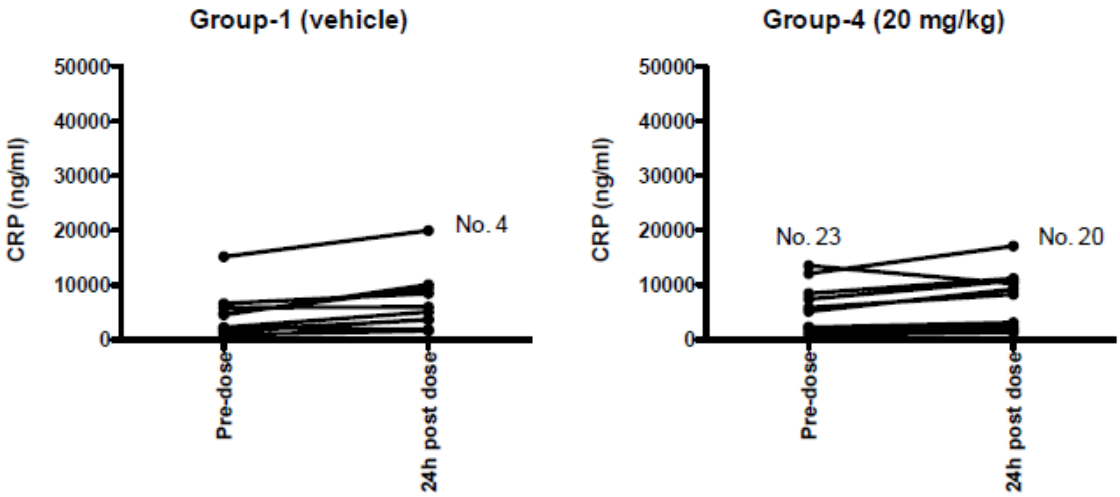
1.60 mg/ml, which is comparable with what have been reported from other studies. Taken together, the results presented indicate an immunological IgA response in at least one dog.

**C-reactive protein analyses**

The aim of the study 2012-29 was to investigate if a single administration of imlifidase in rabbits induced an inflammatory response by comparing the level of serum CRP before treatment to the level 24 hours after the first injection (32 animals divided in four groups, treated with 0, 0.2, 2 or 20 mg/kg imlifidase).

A comparison between the individual pre-dose CRP-levels and the levels in serum collected 24 hours (day 2) after dosing is shown in **Figure 8**.

**Figure 8 CRP-levels after intravenous administration of imlifidase in rabbits.**




Serum CRP-levels measured pre-dose and 24 hours after first dosing. Group-1 (N=10) received vehicle (PBS) and Group-4 (N=10) received 20 mg/kg. None of the tested animals had CRP-values that suggest an on-going or induced inflammatory reaction, but the three animals with the highest CRP are indicated in the figure.

In an additional supplementary study (Study No 2012-028) to the repeat dose toxicity study in the dog (Study No. 2012-012), the level and time course of the acute phase reaction in the dogs were investigated, using CRP as a marker. A clear correlation between animals that developed anti-imlifidase antibodies after dosing and elevation of CRP could not be demonstrated. Dog No. 29 was the only animal that developed anti- imlifidase antibodies after first dosing that also responded with elevated CRP.

## 2.3.5. Ecotoxicity/environmental risk assessment

Imlifidase is a recombinant protein and in accordance with the CHMP guideline on the environmental risk assessment is exempted from environmental risk assessment testing (EMEA/CHMP/SWP/4447/00).

## 2.3.6. Discussion on non-clinical aspects

The pharmacology of imlifidase was well characterized in *in vitro*, *ex vivo* and *in vivo* animal models, namely in the rat and dog species. Results of the provided studies are in line with published literature. Imlifidase cleaves all four human subclasses of IgGs in serum and IgG-type of BCR bound to the cell surface in a two-step reaction into single cleaved IgG (scIgG) and further into the $F(ab')_2$ and Fc

fragments. Imlifidase was also fully active on IgGs from rabbit but only partially cleaved dog IgGs. Therefore, the rabbit was selected as the most relevant species for toxicity studies. Imlifdase does not cleave Ig isotypes IgA, IgE, IgD or IgM and it has been published that IdeS has a high substrate specificity and specifically cleaves IgGs, no off-target cleavage of other proteins is expected.

After cleavage of IgG, the IgG pool is reconstituted and is back at normal levels after ~10 days.

It has been demonstrated that the activity of imlifdase on IgGs is rather $C_{max}$- than AUC-dependent. For the interpretation of toxicity studies of imlifidase, toxicological effects relating to the cleaving activity of imlifidase $C_{max}$ is therefore considered the relevant parameter to determine safety margins. It was demonstrated that exposure of rabbits and dogs to IgG fragments (F(ab')2 and Fc) is lower than in humans. This indicates that rabbits and dogs might not be suitable to detect all IgG fragment-related toxicities as exposure cannot be further forced to higher levels. However, based on available clinical data and absence of major clinical safety concerns the lack of AUC-based safety margins is acceptable. With regards to imlifidase toxicities, it was argued by the applicant that safety margins at the LOAEL (but not the NOAEL) are 3-fold in rabbits and 12-fold in dogs. It is agreed that in relation to the no/low AUC margins at the NOAEL the difference in dose regimen and pre-existence of ADA between rabbit/dogs and humans should be taken in consideration. In addition, based on available clinical data and absence of major clinical safety concerns the lack of AUC-based safety margins for imlifidase is acceptable by CHMP. In addition, it is reassuring that $C_{max}$-based safety margins are sufficiently high.

Imlifidase treatment could reduce the level of IgG antibodies directed against HLA tested positive in human serum. The reduction in the level of functional IgG after imlifidase treatment was reflected in CDC tests against T and B cells (CDC-CXM) from hypothetical donors where the capacity of imlifidase to turn a positive cross-match to negative was also demonstrated. *In vitro* studies on rabbit and human IgG showed that scIgG has impaired Fc-mediated effector functions but may not be completely inactive when present in high concentrations. Thus, dosing with imlifidase should aim at generating the end products (F(ab')2 and Fc) to ensure that all Fc-mediated effector functions are neutralized.It has been demonstrated that ADAs in human serum have neutralizing capacity and bind to the active and inactive part of imlifidase. It has however also been demonstrated that complete cleavage of all IgGs is achieved at similar concentrations independent of ADAs (> 7µg/mL). Therefore, it is supported by CHMP that it is important to reach sufficiently high levels *in vivo* to completely cleave all IgGs and to avoid circulation of scIgG with possible Fc-mediated activity.

Data from the system of purified IgG1 (Humira) indicate that there is an about two-fold potency difference between Process 1 and 2 material. This potency was reduced when human serum was used for potency determination. It is understood that human serum contains ADAs and all subclasses of IgGs which leads to much more variability and consequently higher standard deviations (matrix effects). In performed cell-based functional assays, the potency differences could not be observed anymore. There were also no differences in remaining HLA antibodies in sera after treatment with imlifidase from Process 1 and Process 2 as determined in a single antigen bead assay (HLA-SAB, class I and class II). These data indicated overall that imlifidase dose adjustment in clinical use may not be necessary. PK data from rabbit toxicity studies also indicate that imlifidase from Process 1 and 2 have a similar PK profile, however, no head-to-head comparison using material from both processes has been performed which would usually be required to claim bioequivalence. Therefore, these data can only be seen as supportive.

Pharmacodynamic drug interactions were investigated in terms of cleavage of common IgG antibody-based therapeutics. Relevant cleavage has been detected at clinically relevant doses for medicinal products based on human or rabbit IgG (eg. basiliximab, rituximab, adalimumab, denosumab, belatacept, etanercept). Imlifidase should therefore not be administered concomitantly to these

products and a timeframe after which such products can be re-administered is included in Section 4.5 of the SmPC.

No safety pharmacology studies were conducted to assess the effect of imlifidase on CNS which are usually conducted in rodents or non-human primates. However, since imlifidase is not active in these species, such studies were not considered to be informative. It is agreed by CHMP that it is highly unlikely that imlifidase passes the BBB and therefore no further studies are considered necessary. Reassuringly, there were no signs of CNS toxicities in rabbits during standard observations, however, these studies were not specifically designed to detect any CNS or behavioural effects in the animals, e.g. a functional observational battery (FOB). In dog toxicity studies, minimal inflammatory nerve damage was observed. These findings are probably immune system related and not a direct effect of imlifidase on the nervous system.

***Pharmacokinetics***

No formal PK studies have been performed with imlifidase. PK data of imlifidase were derived from toxicity studies performed in rabbits and dogs. Imlifidase concentration and immunogenicity were initially assessed using ELISA methods, and more recently using ECL based methods. The analytical methods are considered appropriate by CHMP. The analytical methods used in pivotal toxicology were validated.

***Toxicology***

Single and repeat-dose toxicity of imlifidase was evaluated in rabbits and dogs. Duration of studies, administration of imlifidase and choice of animal species were according to the current guidelines. Rabbits and dogs were chosen as animal species, since imlifidase is not active in the rat.

In the GLP compliant repeat-dose studies, imlifidase was given as a slow IV injection at dose levels of 0, 0.2, 2.0 and 20.0 mg/kg in rabbits and dogs, where the lowest dose was demonstrated to be fully pharmacologically active in the rabbit.

Repeat-dose toxicity studies in rabbits and dogs showed that rabbits were found to tolerate four once weekly administrations whereas dogs were only found to tolerate two once weekly administrations; additional administrations resulted in severe hypersensitivity reactions.

Lung findings including increased alveolar macrophages, inflammation, oedema and congestions were observed in rabbit single and repeat-dose toxicity studies. The dose-related lung changes are likely a treatment-related exacerbation of background findings in rabbits. A clear rationale for the lung findings is not presented. However, the applicant considers the pharmacological exacerbation of the lung lesions related to an immediate and large protein burden to the lungs due to the treatment of rabbits with a high infusion rate of imlifidase which is several times higher than that given in humans. In addition, no lung findings were observed in dogs and no signs indicating corresponding findings has been observed in clinical studies. It is therefore agreed by CHMP to consider the observed lung changes specifically related to the rabbit species in combination with high infusion rates of imlifidase, and to consider it as a low safety concern for patients treated with imlifidase.

Heart findings were observed in rabbits with both drug products which appear to be related to high ADA level and immune complex deposition. The applicant initiated a study to evaluate the presence of immune complex deposits in imlifidase treated rabbits with heart findings and provided preliminary data. Preliminary data (tissue staining for IgG and C5b9) were provided. Potential signs of immune-complex deposits (e.g. granular staining of IgG) were present in heart tissue of rabbits, in the high dose group (12 mg/kg) with histological heart findings (myocardial degeneration). It is agreed by CHMP that this may be interpreted as possible presence of immune complex deposits. This is further supported since corresponding IgG granular staining was not observed in control animals and in

animals in other dose groups with no heart findings. However, the IgG stained granules may also represent after IgG cleavage of imlifidase, so further IHC staining (e.g. staining of complement C3 or other appropriate staining) is needed to further support the presence of immune complex deposits. The applicant could not provide a specific mechanism underlying the heart findings but discussed potential mechanisms for possible immune-related events that seem reasonable by CHMP. With regards to the human relevance of the observed heart findings in rabbit, the applicant argues that the preliminary data providing differences in dosing frequencies (4 once weekly doses in rabbits versus the intended 1 single dose and in rare occasions 2 doses in humans), the severity grade and reversibility of the rabbit heart findings and the absence of corresponding effects or signs observed in the clinical programme, support a low risk to the human. This may be considered likely by CHMP although conclusive data from the current immunohistochemical study may be of further support to this assumption. . The final results will be submitted for a conclusive assessment as a recommendation by end of 2021 at the latest. The final data from the present study is considered by CHMP to pose no concern regarding the overall perspectives of benefit/risk balance.

The kidney findings observed in the dog species only (tubular basophilia and interstitial fibrosis), are suggested to represent a treatment-related exacerbation of the background findings occurring commonly in dogs. However, no such findings were recorded in the control groups (main and recovery animals; N=10 out of a total of 32 animals in the study). The applicant refers to publications to show that the observed kidney findings are background findings in beagle dogs. Based on the provided publications, CHMP concurs that these findings occur in beagle dogs, although it cannot be considered as common, which is reflected by the absence of kidney findings in control beagle dogs in the present study. The applicant considers the kidney findings (at least the fibrotic change) not treatment related, this is agreed by CHMP in view of the short time-course of treatment, while fibrosis is generally considered to take time to develop. With regards to tubular basophilia that may be an early manifestation of tubular degeneration, the absence of change in kidney parameters recorded in any of the affected animals indicate limited impact of the observed lesions. Since the kidney findings were observed only in one species and there were no correlation between kidney findings and function, CHMP considers that there is a low safety concern for patients treated with imlifidase.

Effects on the CNS were observed in one animal in the high dose group of study 2012-012. Beagle pain syndrome was diagnosed and an inflammation was most likely present already prior to start of the study. It cannot be ruled out, that the already existing inflammation might have been potentiated by the administration of imlifidase. Based on the findings, it is concluded, that under certain conditions, imlifidase can give immune-mediated reactions. No separate safety pharmacology study was conducted to assess the effect of imlifidase on the CNS. Usually these evaluations are conducted in rodents and can be included for biotech-products into the repeat-dose toxicity studies. However, since imlifidase is not active in these species, such studies were not considered to be informative. The applicant was thus requested to discuss the effects on the CNS in the dog species. No other effects on neurotoxicity further to those reported in the dog of the high dose group were observed in the dog studies. High dose females of study 2012-012 showed an increase in mean body temperature compared to controls. However, when compared to the group mean baseline and 1-hour values no difference in body temperature was observed. It is therefore concluded that in the dog studies, no clinical signs indicative of an effect on the CNS were observed.

The NOAEL in the repeat-dose studies was set at 2 mg/kg in both species. Exposure margins (NOAEL/clinical exposure) relating to $C_{max}$ were 13.4 in rabbits and 5.7 in dogs. Exposure margins corresponding to AUC in rabbits and dogs were 0.41 and 0.86 respectively.

In both animal species, ADA-response was evident. In the dogs, the response was mainly of the IgG class and in the rabbits ADA-response is mainly of the IgM and IgG classes.

Consistent with the origin of imlifidase, no genotoxic liability is expected and in alignment with applicable guidance, no such studies were conducted. Since imlifidase is intended to be used as a single dose, it has not been tested for carcinogenicity, which is agreed by CHMP.

Effects on fertility was assessed by standard examination of male and female reproductive organs in the pivotal repeated dose toxicity studies in rabbits and dogs. In these studies, no changes of the male and female reproduction system were recorded (except for one female rabbit with vascular inflammation in multiple sites including reproductive organs possibly due to immune complex related injury). No comprehensive histopathological examination of male and female reproductive organs was conducted by the applicant, whereas this was advised during protocol assistance if repeat-dose toxicity studies are used to assess effect on fertility. It is therefore concluded that the potential effect of imlifidase on male and female reproductive organs have not been fully addressed and this is clearly stated in the SmPC, section 5.3.

There was no indication of teratogenic effect in an embryofoetal-development toxicity study in rabbits. No pre- and post-natal development studies were performed.

No concern was found in terms of local tolerance based on the outcome in repeat-dose toxicity studies in rabbits and dogs and in the embryo-foetal developmental toxicity study in the rabbits, after intravenous injection of imlifidase.

### 2.3.7. Conclusion on the non-clinical aspects

No obvious hazard of relevance for humans was observed with regard to preclinical secondary and safety pharmacology, pharmacokinetics and toxicology. Final data from immunohistochemical analyses of heart tissue in the rabbit study will be submitted as a post-authorization measures classified as recommendation [REC] by end of 2021 at the latest. The outcome of the non-clinical assessment is considered by CHMP not to have an impact on the overall perspectives of the benefit/risk balance.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Study identifier/ Location of study report | Study objectives | Study design | Treatments | No. of subjects enrolled / completed | Population | Study Status; Type of Report |
|---|---|---|---|---|---|---|
| 11-HMedIdeS-01 | PK, PD, safety | Randomised, placebo-controlled, double-blind dose escalation | Single IV infusion<br>0.010 mg/kg<br>0.040 mg/kg<br>0.12 mg/kg<br>0.24 mg/kg | <br>8<br>4<br>4<br>4 | Healthy men 18-45 years of age | Complete; Full |
| 13-HMedIdeS-02 | Effective dose, PK, PD, and safety | Open label, uncontrolled, non-randomized dose escalation | Single or once repeated[a] IV infusion<br>2×0.12 mg/kg<br>1×0.25 mg/kg<br>2×0.25 mg/kg | <br>3/3<br>3/3<br>2/2 | Men and women diagnosed with CKD stage 5, and HLA sensitized, ≥18 years of age | Complete; Full |
| 13-HMedIdeS-03 | Efficacy, PK, PD, and safety | Open label, uncontrolled, non-randomized dose escalation | Single IV infusion<br>0.25 mg/kg<br>0.50 mg/kg | <br>5/5<br>5/5 | Men and women diagnosed with CKD stage 5, and HLA sensitized, ≥18 years of age | Complete; Full |
| 14-HMedIdeS-04 | Efficacy and safety | Open label, uncontrolled | Single IV infusion<br>0.24 mg/kg | <br>17/17 | Highly sensitized patients with CKD stage 5, and active on the kidney transplant waiting-list | Complete; Full |
| 15-HMedIdeS-06 | Efficacy, PK, PD, and safety | Open label, uncontrolled | Single or once repeated[a] IV infusion<br>1×0.25 mg/kg<br>2×0.25 mg/kg | <br>16/13<br>3/3 | Patients on the kidney waiting-list who have previously undergone unsuccessful desensitization, or in whom effective desensitization is highly unlikely | Complete; Full |
| 17-HMedIdeS-13 | Efficacy and safety | Retrospective study to collect additional donor and recipient data from patients who have been treated with imlifidase prior to kidney transplantation | Not applicable | 11/11 | Men and women transplanted in Study 02 and Study 03 | Complete; Full |
| 17-HMedIdeS-14 | Efficacy and safety | 5 year, long-term follow up, observational study of patients patients who have | Not applicable | Up to 46 planned to be enrolled | Patients who have undergone kidney transplantation after imlifidase administration in | Ongoing; cut off 30-Sep-2019 |

| Study identifier/ Location of study report | Study objectives | Study design | Treatments | No. of subjects enrolled / completed | Population | Study Status; Type of Report |
|---|---|---|---|---|---|---|
| | | undergone kidney transplantation after imlifidase administration | | | studies 13-HMedIdeS-02 or 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06 | |
| 18-HMedIdeS-15 | PD, PK, safety and tolerability | placebo controlled, double-blind, randomized | single IV infusion 1×0.25 mg/kg **Process 2 material** | 15/5 | 20 healthy men aged 18 to 55 years | Complete; Full |

## 2.4.2. Pharmacokinetics

The pharmacokinetics of imlifidase has been studied clinically with 1 or 2 doses ranging from 0.010 mg/kg to 0.50 mg/kg within 5 studies with process 1 material and 1 study with process 2 material. Two studies were conducted in healthy subjects (studies 01, 15) and 4 Phase I/II studies in patients with CKD (Studies 02, 03, 04, 06 and 15).

The clinical studies 01, 02, 03, 04 and 06 were conducted with process 1 material. Study 15 was conducted with process 2 material.

**Methods**

- Bioanalysis of imlifidase

Imlifidase analysis method is a sandwich immunoassay based on ECL as detection system using hen anti-IdeS for capture and a rabbit anti IdeS biotin labelled detection antibody. Readout is provided by a streptavidin sulfotag and MSD measurement. The validation of the imilfidase assay was adequate for the intended purpose; stability of the samples during transport and storage has been demonstrated by stability data.

- Anti-drug antibody analysis

Quantitative determinations of anti-imlifidase IgG and IgE antibodies in human serum from all clinical studies were performed using customised imlifidase-Immuno CAP assays.

No neutralizing antibody assay was presented which was justified by the single dose use of imlifidase. The neutralising potential of pre-dose ADAs may however still be relevant in the case where it may lead to a loss of efficacy. When pre-dose ADA are present, this leads to a lower clearance rate (of the complex) and thereby a higher PD effect. In the case where these ADAs are neutralising, this would lead to an overestimation of the effect.

- Bioanalysis of PD endpoints

*Total IgG*

The methods used for determination of IgG levels available at clinical chemistry laboratories (turbidimetry/nephelometry) do not discriminate between the different IgG-fragments generated post-imlifidase treatment and cannot be used to determine treatment efficacy.

The concentration of IgG in human serum was determined by a sandwich ELISA and later an ECL method. The $(F(ab')_2$ moiety is captured by a goat anti-human IgG $F(ab')_2$ and detection occurs via the

Fc moiety of the IgG molecule. This assay cannot distinguish between intact IgG and scIgG, and the readout is therefore the sum of intact IgG and scIgG.

*IgG fragments*

To monitor IdeS efficacy in serum, an ELISA method based on a Fab-specific capture and an Fcγ-specific detector thereby detecting intact IgG and scIgG was developed.

In the Fcγ assay a goat anti-human IgG (Fcγ fragment specific) F(ab´)2 fragment was used as capture antibody and a biotin conjugated goat anti-human IgG (Fcγ fragment specific) F(ab´)2 fragment as detector. A streptavidin-horseradish peroxidase conjugate was used for secondary detection.

In the Fab assay an affinity purified mouse anti human IgG F(ab')2 fragment specific antibody was used as capture antibody and biotinylated CaptureSelect IgG-CH1 as detector. A streptavidin-horseradish peroxidase conjugate was used for secondary detection.

Visualisation and qualitative analyses of the presence of IgG and IgG fragments in human serum before and after treatment with imlifidase were done using polyacrylamide gel electrophoresis under non-reducing conditions in the presence of sodium dodecyl sulphate (SDS-PAGE). The SDS-PAGE method was supplemented with Western blot analysis using an anti Fc-antibody detecting IgG, scIgG, and Fc-fragment. The method was also used for analysis of IgG fragments in urine for study 06 samples.

PK evaluation was performed using WinNonlin® Professional (Pharsight®, St. Louis, Missouri, USA). An open 2-compartment model was found to best describe the data and was used to describe all clinical studies.

## *Absorption*

Imlifidase is administered as an intravenous infusion. The bioavailability is therefore 100%.

Essential PK data for imlifidase (process 1) is available from study 01 [11-HMedIdeS-01: A phase I, single centre study to evaluate the safety, tolerability and pharmacokinetics of intravenous IdeS after administration of single ascending dose in healthy, male subjects (**Table 12**). Data from Study 15 with process 2 was compared to data from study 01 conducted with process 1 material (**Table 13**). A direct head-to-head comparison with process 1 material was not possible since product from process 1 was no longer available at the time of Study 15 conduct.

**Table 12 PK parameters following a single iv infusion of imlifidase to healthy men and patients with CKD (all process 1 material)**

| | | Study 01 | | Study 02 | | Study 03 | | Study 04 | Study 06 |
|---|---|---|---|---|---|---|---|---|---|
| | | **0.12 mg/kg N=4** | **0.24 mg/kg N=3** | **0.12 mg/kg N=3** | **0.25 mg/kg N=4** | **0.25 mg/kg N=5** | **0.50 mg/kg N=5** | **0.24 mg/kg N=17** | **0.25 mg/kg N=18** |
| **AUC** (h×µg/mL) | Mean (SD) | 130 (43) | 230 (110) | 110 (27) | 340[a] (120) | 210 (120) | 630 (530) | - | - |
| **$C_{max}$** (µg/mL) | Mean (SD) | 3.14 (0.33) | 5.66 (0.61) | 2.24 (0.08) | 6.39 (1.02) | 5.92 (1.19) | 9.92 (0.89) | - | - |
| **$t_{½}$** (h) distribution | Harmonic mean | 4.0 | 2.8 | 4.0 | 6.3 | 5.1 | 6.0 | 4.1 | 4.6 |
| **$t_{½}$** (h) elimination | Harmonic mean | 130 | 110 | 54 | 89 | 74 | 93 | 71 | 76 |
| **CL** (mL/h/kg) | Mean (SD) | 1.1 (0.4) | 1.2 (0.5) | 1.1 (0.3) | 0.7 (0.3) | 1.7 (1.2) | 1.2 (0.8) | 1.9 (1.4) | 1.8 (0.8) |
| **$V_z$** (L/kg) | Mean (SD) | 0.21 (0.07) | 0.20 (0.08) | 0.09 (0.01) | 0.09 (0.02) | 0.17 (0.08) | 0.16 (0.07) | 0.19 (0.11) | 0.20 (0.05) |

[a]Data from 1 outlier (AUC >4×SD outside mean) were excluded

**Table 13 Pharmacokinetic parameters for imlifidase after single IV infusion to healthy subjects with Process 1 (study 01) and Process 2 (study 15) materials**

| Pharmacokinetic Parameter | | Process 1 (Study 01) 0.24 mg/kg (N=3)[1] | Process 2 (Study 15) 0.25 mg/kg (N=13)[1] |
|---|---|---|---|
| $C_{max}$ (µg/mL) | Geometric mean (%CV) | 5.6 (0.11) | 5.8 (21) |
| AUC (h×µg/mL) | Geometric mean (%CV) | 210 (52) | 137 (82) |
| $t_{½}$ (h) distribution phase (α) | Harmonic mean<br>Median | 2.7<br>2.5 | 1.8<br>2.3 |
| $t_{½}$ (h) elimination phase (β) | Harmonic mean<br>Median | 107<br>141 | 89<br>74 |
| CL (mL/h/kg) | Geometric mean (%CV) | 1.1 (40) | 1.8 (82) |
| $V_z$ (L/kg) | Geometric mean (%CV) | 0.19 (41) | 0.20 (67) |

[1] Based on subjects with an acceptable 2-compartment curve fit

A population pharmacokinetic-pharmacodynamic (PKPD) model in patients with end stage renal disease (ESRD) and healthy subjects based on clinical data obtain using process 1 material was provided. The analysis dataset from study 15 was merged with the developed PKPD analysis dataset from studies 01, 02, 03, 04, 06 to describe the difference in PK and PD between imlifidase process 1 material and process 2 material.

The pop PK model (for process 1 material data only) was a 2-compartment model, with linear elimination and a proportional residual error model with pre-ADA and WT as covariates on CL and Vc, respectively. A between study variability in baseline IgG was identified and estimated to 21.5% CV and

a healthy volunteer effect (vs. patients with end-stage renal disease (ESRD)), estimated to a ratio of 4.2 with patients having a lower value.

Simulations for process 2 material are provided in Table 14.

**Table 14 Simulations for process 2 material**

| Dose | Median % with 5% or less of IgG Baseline | 90% CI | Median % with more than 5% of IgG Baseline | 90% CI |
|---|---|---|---|---|
| At 2 hours after dose | | | | |
| 0.12 mg/kg | 72.8 | (71.1 – 74.4) | 27.2 | (26 – 29) |
| 0.25 mg/kg | 97.0 | (96.3 – 98.0) | 3.0 | (2.0 – 3.7) |
| 0.5 mg/kg | 99.9 | (99.7 – 100) | 0.1 | (0.0 – 0.3) |
| At 6 hours after dose | | | | |
| .12 mg/kg | 96.1 | (95.4 – 97.1) | 3.9 | (2.9 – 4.6) |
| 0.25 mg/kg | 99.8 | (99.5 – 100) | 0.2 | (0.0 – 0.5) |
| 0.5 mg/kg | 100 | (99.9 – 100) | 0 | (0.0 – 0.1) |
| At 12 hours after dose | | | | |
| 0.12 mg/kg | 97.2 | (96.4 – 97.9) | 2.8 | (2.1 – 3.6) |
| 0.25 mg/kg | 99.6 | (99.3 – 99.9) | 0.4 | (0.1 – 0.7) |
| 0.5 mg/kg | 99.9 | (99.8 – 100) | 0.1 | (0.0 – 0.2) |
| At 24 hours after dose | | | | |
| 0.12 mg/kg | 96.1 | (95.3 – 96.9) | 3.9 | (3.1 – 4.7) |
| 0.25 mg/kg | 99.1 | (98.6 – 99.5) | 0.9 | (0.5 – 1.4) |
| 0.5 mg/kg | 99.8 | (99.5 – 99.9) | 0.2 | (0.1 – 0.5) |
| At 48 hours after dose | | | | |
| 0.12 mg/kg | 94.2 | (93.4 – 95.3) | 5.8 | (4.7 - 6.6) |
| 0.25 mg/kg | 98.2 | (97.6 – 98.8) | 1.8 | (1.2 - 2.4) |
| 0.5 mg/kg | 99.5 | (99.1 – 99.7) | 0.5 | (0.3 – 0.9) |

- Bioequivalence

No *in vivo* PK studies were performed to assess bioequivalence of process 1 & 2 drug product. The bioequivalence assessment relies solely on PD *in vitro* markers, which provide inconsistent data between the IgG ECL immunoassay and the spike in SDS-PAGE assay.

## *Data from food-interaction studies*

Imlifidase is administered as an intravenous infusion. No effect of food is anticipated.

## *Distribution*

The serum concentration time curve of imlifidase can be described as bi-phasic curve with a short distribution phase half-life.

The elimination of imlifidase was characterized by an initial distribution phase with a mean half-life of 4.3 (1.0 -16) hours for process 1 material and 1.8 (0.6-3.6) hours for process 2 material. The distribution volume during elimination phase (Vz) was 0.16 L/kg (0.066-0.44) for process 1 material and 0.20 (0.06-0.55) L/kg for process 2 material.

Volume of the central compartment is the initial volume, in which Imlifidase distributes, directly after infusion. In study 02, the determined volume of the central compartment of the 2-compartment model

was 0.046 mL/kg. This volume is approximately 4.6% of the body volume and thereby similar to the plasma volume.

Comparison of distribution volume between healthy subjects and patients did not show any differences.

The similar size of volume of distribution at steady state and volume distribution during elimination phase of imlifidase across the studies indicates that imlifidase is close to distribution equilibrium between plasma and tissues during the elimination phase.

The observed maximum concentration ($C_{max}$) values were also close to proportional to the dose over the dose range investigated.

### *Elimination*

The elimination of imlifidase in all studies was described by an open 2-compartment model. At comparable doses and across studies the elimination of imlifidase was comparable in healthy subjects and patients.

The clearance showed also similar values for healthy subjects and patients across the studies.

The elimination is characterised by a slower phase with a mean half-life of 78 hours (30-337) or 89 (60-238) hours, for process 1 or 2 material, respectively. The mean clearance (CL) was 1.3 mL/h/kg (0.25-5.7) or 1.8 (0.6 7.9) mL/h/kg for process 1 or 2 material, respectively. Because of the nature of imlifidase, elimination is expected to occur by proteolysis.

### *Dose proportionality and time dependencies*

- Single dose

The exposure to imlifidase increased proportionally after a single intravenous infusion of 0.12 to 0.5 mg/kg body weight over 15 minutes. Dose proportionality is given based on $C_{max}$ but not based on AUC.

The effect of pre-dose ADAs on the elimination (CL) has been shown to be statistically significant, with a decreased CL for higher ADA levels, both in the Spearman correlation and in the pop PK model.

A higher variability of AUC may be caused by pre-dose ADAs, but the PK of imlifidase can be considered dose proportional between 0.12 and 0.50 mg/kg.

The time dependency of the elimination of imlifidase i.e. PK upon repeated administration has not been specifically addressed since imlifidase is intended for a single administration with the possibility of repetition within 24 hours, and is not indented for repeated treatments. Since ADA is cleaved within few hours of imlifidase administration together with the pool of IgG and does not revert until 1-2 weeks after administration together with intact IgG, any ADA-related elimination time dependency on a 2nd dose administered within 24 hours is regarded highly unlikely by the applicant.

- Intra- and inter-individual variability

During development, it was demonstrated that the effect of the imlifidase dose is dependent on the level of neutralising ADA present at the time of dosing. The vast majority of all people have been infected by *S. pyogenes*, and therefore have circulating pre-formed antibodies towards imlifidase, albeit at varying concentrations, in their blood. These antibodies can potentially neutralise the effect of imlifidase, and the effective dose therefore has to be high enough to overcome any neutralising capacity of ADA. The dose selected during development (0.25 mg/kg) is a dose that in all tested

subjects resulted in complete cleavage of IgG to F(ab')2 and Fc within few hours in the presence of varying amounts of naturally occurring ADA.

- Pharmacokinetics in target population

Study 01, in healthy volunteers, and study 2, in CKD patients, were used for comparing PK parameters. While $C_{max}$, half-life and clearance are of similar size in the two studies, the average volume of distribution at steady-state in the patient group was less than half that of the healthy group. The remaining studies in CKD patients delivered similar observed PK parameters that were fitted using the same two compartment model.

The applicant presented a comparison of volumes of distribution and explained the lower Vz in study 02 by the possible effect of dialysis on body fluid balance.

## *Special populations*

- Renal impairment

Renally impaired patients constitute the target population. The pharmacokinetics of imlifidase were comparable in healthy subjects and patients with chronic kidney disease.

- Hepatic impairment

No patients with moderate or severe hepatic impairment were studied in renal transplant protocols.

- Gender

Of the 46 subjects administered at least 0.12 mg/kg imlifidase, 25 were men and 21 were women. A comparison of the PK parameters (distribution and terminal t½ and clearance) does not indicate any effect of gender.

- Weight

Since total IgG amounts are weight proportional, dosing is based on body weight (0.25 mg/kg).

- Elderly

Data on the use of patients older than 65 years are limited (3 patients), but there is no evidence to suggest that dose adjustment is required in these patients.

- Children

No data are available in children. Two studies are planned to be conducted as part of the agreed PIP (EMEA-002183-PIP01-17) to evaluate efficacy and safety and establish the PK profile of imlifidase in children aged from 1 to less than 18 years with CKD.

## *Pharmacokinetic interaction studies*

Imlifidase is a cysteine protease that specifically cleaves IgG. The species specificity results in degradation of all subclasses of human and rabbit IgG. As a consequence, IgG-based medicinal products may be degraded and inactivated if given in connection with imlifidase (see Non-clinical aspects Section 2.3).

## 2.4.3. Pharmacodynamics

### *Mechanism of action*

Imlifidase is an immunosuppressant (ATC code proposed by WHO L04AA41) that cleaves IgG in the lower hinge region in a two-step reaction. It first cleaves one of the heavy chains generating a single cleaved IgG molecule (scIgG) which introduces a conformational change, and then cleaves the remaining heavy chain, leading to a F(ab')2 fragment and a dimeric Fc fragment. The F(ab')2 fragments generated by imlifidase-specific degradation of IgG retain full binding capacity to epitopes but are unable to participate in Fc mediated activities. Imlifidase is highly specific towards all four subclasses of human IgG. Other Ig molecules, i.e. IgA, IgD, IgE and IgM are not cleaved. IgG antibody levels return to normal levels in approximately 2-3 weeks. According to the applicant, the treatment with imlifidase cleaves the entire pool of IgG, including DSAs, within 6 to 24 hours, thereby reducing the serum levels of DSA to achieve crossmatch conversion, allowing transplantation to proceed.

### *Primary and Secondary pharmacology*

The PD of imlifidase process 1 was investigated *in vitro/ex vivo* (on human IgGs and human sera) and in the clinical Studies 01, 02, 03, 04 and 06.The effect of imlifidase to cleave the pool of IgG, including DSAs, was evaluated, as well as the ability of imlifidase to convert a positive crossmatch to negative within 24 hours to make the patient eligible for kidney transplantation.

The dose levels throughout development have been selected to obtain the intended pharmacological effect of imlifidase treatment, i.e. complete cleavage of IgG into F(ab')2 and Fc. Complete cleavage of IgG into F(ab')2 and Fc is desired since scIgG interferes with many of the assays used in clinical practice in connection with transplantation, e.g. the single antigen bead assay (SAB-HLA), the flow cytometry crossmatch (FCXM) test, and the total IgG assay used in clinical practice.Intravenous administration of imlifidase induced a rapid decline of the serum concentration of IgG in healthy men as well as in patients with CKD, with signs of elimination evident already after 1 hour at the dose levels 0.12-0.50 mg/kg. The rate of decline in IgG and the maximal effect obtained were comparable within the same dose between the studies (**Table 15**), but increasing the dose from 0.12 to 0.24/0.25 mg/kg increased both the cleavage rate and the maximal effect. Since a rapid cleavage was obtained with 0.24/0.25 mg/kg, increasing the dose further to 0.50 mg/kg only showed marginal additional effect. Maximal effect on IgG concentration was reached within 6 hours in Study 02 and Study 03, and within 24 hours in Study 04 and Study 06, with the small amounts remaining representing scIgG and not intact IgG. Thus, in both healthy subjects and patients with CKD, imlifidase induced a dose dependent and reversible rapid decrease of the IgG levels. The IgG levels started to increase in both healthy subjects and patients 4 to 7 days after administration of 0.24/0.25 mg/kg.

The applicant clarified that the apparently slow cleavage of IgG after 0.12 mg/kg in Study 02 is due to 1 of the 3 subjects showing deviant IgG levels, the IgG concentration measured at 1 hour actually being higher than the baseline value. At 6 hours, the fraction of remaining single-cleaved IgG (scIgG) is comparable between Studies 01 and 02.

**Table 15 Percentage IgG cleaved to Fc and F(ab')2 by time in response to a single IV infusion of imlifidase to healthy subjects and patients with CKD**

| | Study 01 | | Study 02 | | Study 03 | | Study 04 | Study 06 |
|---|---|---|---|---|---|---|---|---|
| Time | 0.12 mg/kg N=4 Mean (SD) | 0.24 mg/kg N=3 Mean (SD) | 0.12 mg/kg N=3[a] Mean (SD) | 0.25 mg/kg N=4[a] Mean (SD) | 0.25 mg/kg N=5 Mean (SD) | 0.50 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 | 0 | 0 |
| 1 hour | 40 (21) | 73 (4) | 6 (45) | 66 (14) | 81 (6) | 86 (14) | 51 (27) | - |
| 2 hours | 67 (9) | 89 (2) | 23 (19) | 92 (6) | 95 (3) | 96 (2) | - | 85 (14) |
| 4 hours | - | - | 65 (22) | 95 (6) | 98 (2) | 98 (1) | - | - |
| 6 hours | 89 (3) | 94 (2) | 81 (11) | 98 (2) | 98 (2) | 99 (1) | 89 (9) | 93 (8) |
| 8 hours | - | - | 85 (11) | 98 (2) | 98 (1) | 99 (1) | - | - |
| 24 hours | 94 (5) | 94 (2) | 94 (3) | >99 (0) | 99 (1) | 99 (1) | 94 (6) | 95 (5) |
| 2 days | 88 (3) | 93 (3) | - | - | >99 (0) | 99 (1) | - | 93 (7) |
| 3 days | - | - | - | - | 99 (2) | 98 (2) | - | - |
| 4 days | 86 (5) | 91 (5) | - | - | - | - | - | - |
| 7 days | 79 (6) | 82 (9) | - | - | 95 (3) | 90 (10) | 80 (36) | 92 (7) |

[a]First dose only
[b]3 subjects received 2 doses 12-20 hours apart

The cleavage of IgG to scIgG and further to F(ab')2 was also followed by analysis of serum samples using SDS-PAGE (**Table 16**). The rapid initial cleavage of IgG started immediately since no patient had intact IgG at the end of the 15-minute infusion. One hour after administration of 0.24/0.25 mg/kg imlifidase, some patients showed only the F(ab')2 fragment, and 2 hours after administration the majority of the patients showed only the F(ab')2 fragment. The observations were similar between the studies, though the cleavage appeared to be somewhat slower in studies Study 04 and Study 06 conducted in patients.

**Table 16 Number of subjects with SDS score after a single IV dose of 0.24/0.25 mg/kg imlifidase**

| | Study 02 Score | | | | | | Study 03 Score | | | | | | Study 04 Score | | | | | | Study 06 Score | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time | 5 | 4 | 3 | 2 | 1 | 0 | 5 | 4 | 3 | 2 | 1 | 0 | 5 | 4 | 3 | 2 | 1 | 0 | 5 | 4 | 3 | 2 | 1 | 0 |
| 0h n=43 | 4 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 17 | - | - | - | - | - | 17 | - | - | - | - | - |
| 0.25h n=9 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | - | - | - | - | - | - | - | - | - | - | - | - |
| 1h n=26 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | | 4 | 12 | 1 | 0 | - | - | - | - | - | - |
| 2h n=27 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 1 | 4 | 0 | - | - | -- | - | - | - | 0 | 0 | 0 | 3 | 15 | 0 |
| 6h n=43 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 6 | 10 | 0 | 0 | 0 | 0 | 3 | 15 | 0 |
| 24h n=44 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 1 | 16 | 0 | 0 | 0 | 0 | 0 | 18 | 0 |
| 48h n=26 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | - | - | - | - | - | - | 0 | 0 | 0 | 0 | 17 | 0 |
| 7d n=41 | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 | 1 | 0 | 0 | 0 | 13 | 0 | 0 | 0 | 0 | 5 | 12 |

5=Intact IgG; 4=Mix Intact and scIgG; 3=ScIgG; 2=Mix ScIgG and Fab; 1=Fab; 0=Lack of IgG, scIgG and Fab fragments

Relationship between plasma concentration and effect

The dose levels throughout development have been selected to obtain the intended pharmacological effect of imlifidase treatment, i.e. complete cleavage of IgG into F(ab')2 and Fc. Complete cleavage of IgG into F(ab')2 and Fc is desired mainly since scIgG interferes with many of the assays used in clinical practice in connection with transplantation, e.g. the single antigen bead assay (SAB-HLA), the flow cytometry crossmatch (FCXM) test, and the total IgG assay used in clinical practice.

The non-clinical studies showed that the effect of imlifidase was concentration-dependent rather than exposure-dependent. This is understood in the way that effects (in animals [and humans]) depend on Cmax rather than on AUC, and the dose required for complete cleavage of IgG was identified in non-clinical models as 0.25 mg/kg single dose.

PK and PD data on proportion of IgG uncleaved and cleaved from phase 1 study (Study 1) conducted with process 2 material(Study 15), is compared to data from study 01 conducted with process 1 material were provided during the procedure and are summarised in **Table 17**.

**Table 17 Proportion (%) of IgG (uncleaved and cleaved) remaining at different timepoints after a single IV infusion of imlifidase process 1 vs. process 2 to healthy subjects (Study 1 vs. Study 15)**

| Time | Process 1<br>0.24 mg/kg<br>(N=4)<br>Mean (SD) | Process 2<br>0.25 mg/kg<br>(N=15)<br>Mean (SD) |
|---|---|---|
| Baseline | 100 | 100 |
| 1 hour | 27 (4) | 5 (3) |
| 2 hours | 11 (2) | 2 (1) |
| 4 hours | | 1 (0) |
| 6 hours | 6 (2) | 1 (0) |
| 8 hours | | 1 (1) |
| 24 hours | 6 (2) | 2 (2) |
| 2 days | 7 (3) | 4 (6) |
| 3 days | | 6 (8) |
| 4 days | 9 (5) | 8 (9) |
| 7 days | 18 (9) | 14 (12) |
| 14 days | 49 (38) | 61 (38) |

The administration of imlifidase resulted in a rapid cleavage of IgG to Fc and F(ab')2 fragments, showing that the pharmacodynamics with the Process 2 material is comparable to the data generated with Process 1 material in Study 01 (**Table 18**).

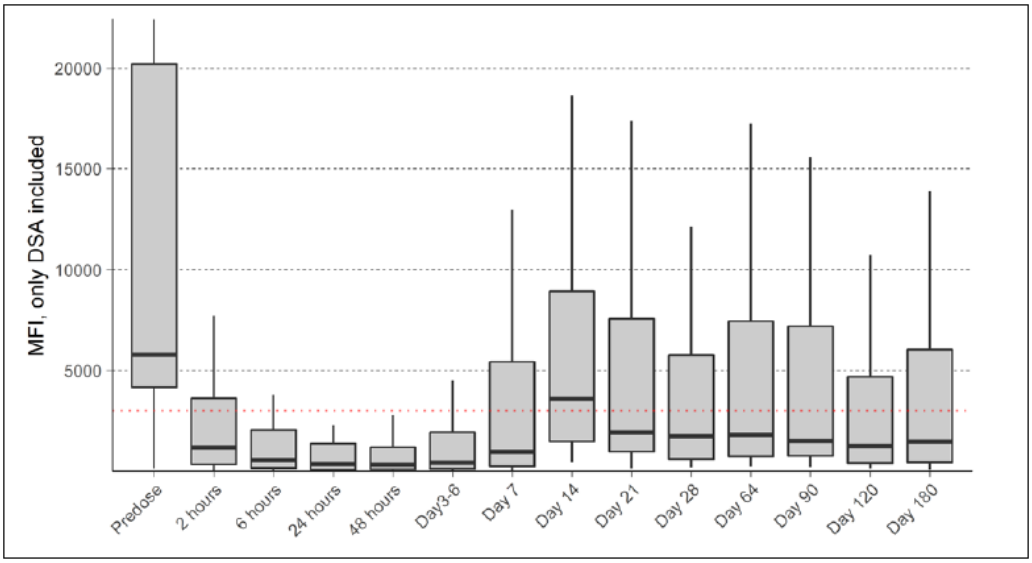
**Table 18 Number of subjects with SDS score after a single IV dose of 0.24/0.25mg/kg imlifidase**

| Healthy subjects (Study 15) Score | | | | | | | Patients (Studies 03, 04, 06) Score | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time | 5 n (%) | 4 n (%) | 3 n (%) | 2 n (%) | 1 n (%) | 0 n (%) | Time | 5 n (%) | 4 n (%) | 3 n (%) | 2 n (%) | 1 n (%) | 0 n (%) |
| 0h n=15 | 15 (100) | 0 | 0 | 0 | 0 | 0 | 0h n=43 | 43 (100) | 0 | 0 | 0 | 0 | 0 |
| 0.25h n=15 | 0 | 0 | 0 | 15 (100) | 0 | 0 | 0.25h n=9 | 0 | 0 | 5 (56) | 4 (44) | 0 | 0 |
| 1h n=15 | 0 | 0 | 0 | 8 (53) | 7 (47) | 0 | 1h n=26 | 0 | 0 | 4 (15) | 19 (73) | 3 (12) | 0 |
| 2h n=15 | 0 | 0 | 0 | 0 | 15 (100) | 0 | 2h n=27 | 0 | 0 | 0 | 4 (15) | 23 (85) | 0 |
| 6h n=15 | 0 | 0 | 0 | 0 | 15 (100) | 0 | 6h n=43 | 0 | 0 | 0 | 9 (21) | 34 (79) | 0 |
| 24h n=15 | 0 | 0 | 0 | 1 (7) | 14 (93) | 0 | 24h n=44 | 0 | 0 | 0 | 1 (2) | 43 (98) | 0 |
| 48h n=15 | 0 | 1 (7) | 0 | 1 (7) | 12 (80) | 1 (7) | 48h n=26 | 0 | 0 | 0 | 0 | 26 (100) | 0 |
| 7d n=15 | 3 (20) | 5 (33) | 7 (47) | 0 | 0 | 0 | 7d n=41 | 2 (5) | 1 (2) | 0 | 0 | 8 (20) | 30 (73) |

Score: 5=Intact IgG
4=Mix Intact and scIgG
3=scIgG
2=Mix scIgG and Fab
1=Fab
0=Lack of IgG, scIgG and Fab fragments

In Study 06, many but not all of the pre-formed DSA rebounded 7-14 days post-imlifidase treatment. SAB-HLA analyses of the DSA profiles show that the specificity of DSA overall was very similar before and after the imlifidase treatment and transplantation (**Figure 9**).

**Figure 9 Median sum of DSA in patients pre- and post-imlifidase and transplantation in Study 06**




Only DSA above MFI3000 are included

## Immunogenicity

Samples from all the 20 healthy subjects and the 54 CKD patients treated with imlifidase in the studies have been analysed with respect to presence of anti-imlifidase antibodies, and all but one were also followed for post-dose changes.

Imlifidase-ImmunoCAP (Thermo Fisher Scientific/Phadia) assays that specifically quantify IgG (LLOQ 2 µg/mL) and IgE (LLOQ 0.1 kU/L) antibodies towards imlifidase in human plasma/serum samples have been developed.

*Presence of anti-imlifidase antibodies before and after administration of imlifidase*

The majority of the healthy study subjects presented an increase of anti-imlifidase IgG after administration of imlifidase process 1. The response was not detectable 1 week after dosing, but reached peak levels around 2 weeks after dosing with a subsequent slow decline. Although the individual variation in the magnitude of the anti-imlifidase IgG response was large, the response was significantly stronger among the subjects receiving 0.12 or 0.24 mg/kg imlifidase compared with subjects receiving 0.01 or 0.04 mg/kg. On day 182, the anti-imlifidase IgG levels for 16 out of 17 follow-up individuals dosed with imlifidase had returned to within the screening range of healthy subjects.

All patients were screened for anti-imlifidase IgG and IgE antibodies predose. All patients had anti-imlifidase IgG antibodies, (median concentration [µg/mL]: Study 02: 11, Study 03: 8, Study 04: 8, Study 06: 8.6), but none had any detectable anti-imlifidase IgE antibodies.

The median predose level of anti-imlifidase IgG in patients with CKD was similar to that observed in healthy subjects, 11 µg/mL (range 2-22 µg/mL). In patients who did not undergo transplantation in Study 02, an increase in anti-imlifidase IgG could be detected from Day 7 with the highest concentrations (range 190-2600 µg/mL) on day 14. Two months after dosing, the levels of anti-imlifidase IgG had started to decrease. No difference in anti-imlifidase IgG response was seen between individuals that had been dosed with 1 or 2 doses, or between dose levels.

Patients who were transplanted showed the highest concentration (up to 4200 µg/mL) of anti-imlifidase IgG on average 1-2 months after treatment both with 0.25 as well as 0.50 mg/kg, with subsequent decline in all patients. The delayed response in transplanted patients compared with healthy subjects and non-transplanted patients is likely due to the immunosuppressive treatment that the transplanted patients receive. The levels of anti-imlifidase IgG on day 180 were higher compared with the predose levels with no apparent dose relationship.

Immunogenicity against process 2 material was evaluated in Study 15. Immunogenicity against process 2 material was in the same range as for process 1 material, with 190-2600 mg/L and 99-4230 mg/L (median 1121 mg/L) anti-imlifidase antibodies at the peak at day 14 for process 1 and 2, respectively. For both material sources, antibodies decreased similarly after day 14.

*Effect of anti-imlifidase antibodies on PD effect*

The presence of ADAs and their likely neutralizing capacity have a negative impact on effects of imlifidase. The lowest imlifidase concentration needed to cleave the first heavy chain and generate a scIgG product is low enough to potentially be affected by the level of neutralizing ADA, while the imlifidase concentration needed to generate F(ab')2 and Fc fragments from the scIgG, on all human IgG subclasses, is much higher. Thus, this further processing of scIgG substrates to F(ab')2 and Fc is less affected by (neutralizing) ADAs since it needs several-fold higher imlifidase concentrations compared with the first step cleaving intact IgG, generally overcoming any effect of ADA present in the patient.

The long-term levels of ADA and the concomitant impact on imlifidase activity, in case of re-transplantation, are currently not known.

As previously found with healthy subjects and patients, the development of anti-imlifidase IgG antibodies after administration of imlifidase process 2 varied largely between the subjects (Study 15). The response was in most subjects not detectable one week after dosing but had reached peak or close to peak levels two weeks after dosing. On Day 14 the median level of all subjects dosed with imlifidase was 1120 mg/L (range: 99-4251 mg/L). In some subjects the levels started to abate already after two weeks, and in almost all subjects after 3 weeks. Thus, the overall picture of anti-imlifidase antibody response in study 15 is comparable to what was reported with process 1 material in Study 01.

## 2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The main PK data of process 1 imlifidase are derived from healthy subjects (**study 01**) with supportive data from CKD patients in phase I/II studies (**studies 02, 03, 04** and **06**). As no phase III studies have been conducted, no PK data is available from phase III studies. Since PK data were initially only available for process 1 material but not for process 2 material, which is the material intended for marketing, the applicant was asked to address the potential impact of differences between process 1 and process 2 material on clinical PK (in humans) and its relevance for patients.Data from a new phase 1 study performed in healthy subjects with process 2 material have been provided (**study 15**) which allowed to characterize the impact of imlifidase from process 1 versus process 2 material on PK and PD.

During the procedure, the applicant submitted the clinical study report for **study 15** with process 2 material. The exclusion criterion (anti-imlifidase IgG >22 mg/L) was considered problematic by CHMP, since patients will not be tested for their anti-imlifidase levels prior to administration of imlifidase. The applicant provided the information that only two subjects had pre-dose anti-imlifidase antibodies > 22 mg/L in imlifidase studies, and for both patients, a single dose of 0.25 mg/kg imlifidase process 1 material resulted in a negative crossmatch. While the exclusion of subjects with pre-dose anti-imlifidase IgG >22 mg/L in **study 15** is unfortunate, the totality of data suggests that data from process 1 material in subjects with pre-dose anti-imlifidase IgG >22 mg/L can be extrapolated to process 2 material. Process 2 material can be expected to be at least as effective as process 1 material, irrespective of the level of pre-dose anti-imlifidase IgG.

The applicant used a PK/PD model to support the dose selection of process 2 material. The assumption that an IgG level below 5% from baseline is likely to induce a negative crossmatch is acceptable by CHMP. The applicant has clarified their modelling approach and provided an updated modelling report that included simulations at different timepoints. The model itself was however not updated. The applicants' choice not to update the model and not to perform a new covariate analysis are not supported by CHMP. The model, as depicted by the provided VPCs, can however reasonably well describe the early timepoints of **study 15** imlifidase PK, and the IgG concentration. The model is not able to adequately describe the late time points of **study 15** imlifidase PK. It is thus acceptable to use the model for the simulations at early timepoints. The model parameters should however not be used to draw any mechanistic conclusions.

The simulations of remaining IgG fraction expected to translate in a negative crossmatch at the intended dose of 0.25 mg/kg of process 2 material indicate that a negative crossmatch is expected from 2h to 48h after the dose in at least 97% of the patients. The dose of process 2 material (0.25 mg/kg) is therefore acceptable to CHMP.

Immunogenicity against process 2 material was in the same range as for process 1 material, with 190-2600 mg/L and 99-4230 mg/L (median 1121 mg/L) anti-imlifidase antibodies at the peak at day 14 for process 1 and 2, respectively. For both material sources, antibodies decreased similarly after day 14. The immunogenicity of both material sources can be considered similar.

According to the guideline on immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev1), an appropriate strategy for immunogenicity assessment is expected. This would typically entail a multi-tiered approach with a screening assay with defined cutpoint, a confirmation assay, a titre determination, a determination of the persistence and neutralizing capacity of the ADA. The applicant did not present a neutralizing antibody assay, which was justified by the single dose use of imlifidase. The neutralising potential of pre-dose ADAs may however still be relevant in the case where it may lead to a loss of efficacy. When pre-dose ADA are present, this leads to a lower clearance rate (of the complex) and thereby a higher PD effect. In the case where these ADAs are neutralising, this would lead to an overestimation of the effect. However, the lack of a neutralising assay is acceptable by CHMP, since the crossmatch status is directly monitored and crossmatch conversion from positive to negative should be confirmed before transplantation.

The validation of the imlifidase assay was adequate and showed that the assay is suitable for the intended purpose; stability of the samples during transport and storage has been adequately demonstrated by stability data.

Dose proportionality is observed for Cmax but not for AUC. The effect of pre-dose ADAs on the elimination (CL) has been shown to be statistically relevant, with a decreased CL for higher ADA levels. The lack of information on time dependency is acceptable to the CHMP in view of the single administration (one or two doses) of imlifidase. A higher variability of AUC may be caused by pre-dose ADAs, but the PK of imlifidase can be considered dose proportional between 0.12 and 0.50 mg/kg.

Volumes of distribution are decreased in the target population compared to healthy humans which was explained by the lower Vz in **study 02** and the possible effect of dialysis on body fluid balance.

Imlifidase cleaves IgG and has been shown to degrade IgG-based medicinal products. Imlifidase should therefore not be administered concomitantly to these products and a timeframe after which such products can be re-administered is included in Section 4.5 of the SmPC.

Pharmacodynamics

The pharmacodynamic action of Imlifidase was well characterized in *in vitro, ex vivo* and *in vivo* animal models.

In humans, the primary pharmacology of imlifidase was investigated in *in vitro/ex vivo* (on human IgGs and human sera) and *in vivo* in the clinical **studies 01, 02, 03, 04 and 06**.

Imlifidase cleaves all four human subclasses of IgGs in serum and IgG-type of BCR bound to the cell surface in a two-step reaction into single cleaved IgG (scIgG) and further into the F(ab')2 and Fc fragments. It is agreed by CHMP that the MoA, cleavage of IgGs, confers the desired clinical effect, i.e. crossmatch conversion. All clinical studies in the development investigated this PD endpoint. It is also agreed by CHMP that imlifidase treatment just prior to transplantation has the potential to transiently desensitize highly sensitized patients; therefore, a proof of concept has been adequately shown.

A formal PK/PD relationship has not been established, despite PD endpoints in the same matrix as PK endpoints.

Data from the phase 1 study with process 2 material (**study 15**) show that PD effect with the Process 2 material is comparable to the that of with Process 1 material observed in **study 01**.

Analysis of IgG and IgG fragments by SDS-PAGE show that intact IgG disappear rapidly, and already at 2 hours no intact nor single-cleaved IgG could be detected on the gel. The disappearance of IgG and scIgG on the gels appears to be slightly faster in healthy subjects compared to patients, which is consistent with the IgG assay and the PK/PD model simulations performed.

The applicant acknowledged that DSA that recur post-transplantation (i.e. in this case, DSA that return within 1 week after treatment with imlifidase) are considered a risk factor for developing transplant glomerulopathy and subsequent graft loss. However, SAB-HLA analyses of the DSA profiles show that the specificity of DSA overall is very similar before and after imlifidase treatment and transplantation.

Imlifidase's effect of IgG cleavage on immunisation status of patients was questioned. The levels of antigen-specific IgG increased to approximately 60-80% of pre-treatment levels within the first 4 weeks post-treatment, and thereafter continued to rise at a somewhat slower rate. The subject's ability to respond and react to specific antigens reverted to the previous state. No off-target biochemical interactions or physiological effects resulting from such interactions had been identified. Upon request by CHMP, the applicant implemented a warning to the SmPC (Section 4.4) regarding the risk for temporary reduction of vaccine protection for up to 4 weeks following imlifidase treatment.

The presence of anti-imlifidase antibodies before and after administration of imlifidase has been investigated. Since imlifidase is generally administered as a single intravenous infusion and only exceptionally a second dose may be given to achieve CXM conversion, the presented analysis concerning ADA is considered adequate.

Most humans have been infected with *S. pyogenes* and antibodies against imlifidase are common. Assessment of IgG in 208 healthy subjects, showed that > 95% of the individuals were positive for ADA (anti-imlifidase IgG) over the range 2-91 mg/L. However, the applicant clarified that since imlifidase is fpr a single use, and since the ADA start to re-emerge not earlier than 1-2 weeks after administration, the titre of ADA and the possible occurrence of neutralising antibodies after administration has no consequences on the efficacy of imlifidase prior to transplantation. It is agreed by CHMP that there is no need for immunogenicity assessment.

## 2.4.5. Conclusions on clinical pharmacology

The main clinical pharmacological aspects of imlifidase after single administration (one or two doses) have been characterised.

Data from the phase 1 **study 15** with process 2 material has been provided showing that the PD effect of Process 2 material is comparable to that of Process 1 material observed in **study 01**. While the exclusion of subjects with pre-dose anti-imlifidase IgG >22 mg/L in **study 15** is unfortunate, the totality of data suggest that data from process 1 material in subjects with pre-dose anti-imlifidase IgG >22 mg/L can be extrapolated to process 2 material.

The posology of single dose administration of 0.25mg/kg and the possibility for a second administration in case crossmatch conversion could not be achieved with a single dose is endorsed by CHMP.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response studies

The selection of imlifidase doses for Phase II investigations was based on data from 20 healthy men in a single phase I study (Study 01), a randomized, placebo-controlled (within each cohort) dose escalation study. This study was terminated (prematurely) testing the dose of 0.24 mg/kg as the highest dose, although the anticipated doses (=planned doses) were set much higher, i.e. up to 1.2 mg/kg of imlifidase.

In a phase II study (Study 02), different dosing regimens of imlifidase were investigated with the objective to find a regimen that decreased the anti-HLA IgG antibodies to a level that allowed transplantation in the majority of patients.

***Study 02: A phase II study to evaluate the safety, tolerability, pharmacokinetics and efficacy of intravenous IdeS after administration of ascending doses in chronic kidney disease patients***

The study was non-randomised, single centre (Uppsala, Sweden) and ascending dose.

Dose selection

The choice of doses in this study was based on the results from the first study in humans (Study 01), performed with healthy subjects. The study 01 was terminated (prematurely) testing the dose of 0.24 mg/kg as the highest dose, although the planned doses were higher, i.e. up to 1.2 mg/kg of imlifidase.

Dose escalation in the study 02 was performed by doubling the chosen doses for each dose group with the anticipated doses 0.12 (group 1), 0.25 (group 2), 0.5 and 1.0 mg/kg given once or twice. The two highest doses were optional and not used.

The study population included patients with Chronic Kidney Disease requiring dialysis and on waiting list for kidney transplantation, and with at least two identified HLA antibodies had to be present of which at least one was 3,000 MFI (Median Fluorescence Intensities) or more as measured by Single Antigen Beads (SAB) assay on at least two occasions.

Upon request by CHMP, the applicant clarified that donor tissue/cells for the CXMs investigated within in Study 02 had been derived from a panel of 30 healthy subjects (blood donors) who together have a human leucocyte antigen (HLA) pattern that represents that of the geographic region. Blood donors with HLA phenotypes which the study patients had antibodies against (donor-specific antibodies) were used for crossmatch analyses in a CDC crossmatch assay. No actual living or deceased donors were used for these analyses. For one patient (patient 02-102), a kidney from a deceased donor became available 17 hours after the second dose of imlifidase. Cells from the deceased donor were used for the CDC and flow cytometry crossmatch test. At that timepoint, serum from the patient 6 hours after the second dose of imlifidase was used for the crossmatch tests.

The patients were followed until day 64 after infusion.

A total of 6-12 subjects were planned for inclusion (N=2 per dosing regimen with possibility to include extra subjects for safety or efficacy reasons).

Transplantation was not part of the study, but was not precluded.

Given the exploratory nature of the study, no formal statistical hypothesis testing was performed in this study and the sample size was not based on formal statistical considerations.

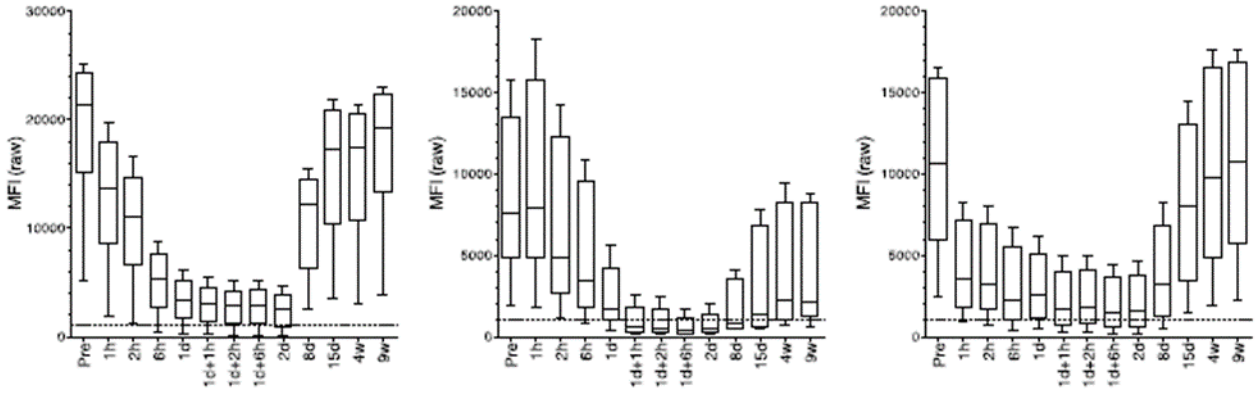
The primary endpoint, defined as IdeS dosing scheme resulting in HLA antibody levels which are acceptable for transplantation, was a combination of the results from the SAB-HLA assay and a complement-fixating (Clq) anti-HLA assay. For a patient to be assessed as having acceptable MFI in the SAB-HLA assay, the 90th percentile MFI for the HLA values should be <1,100 at one timepoint within 24 hours after IdeS treatment.

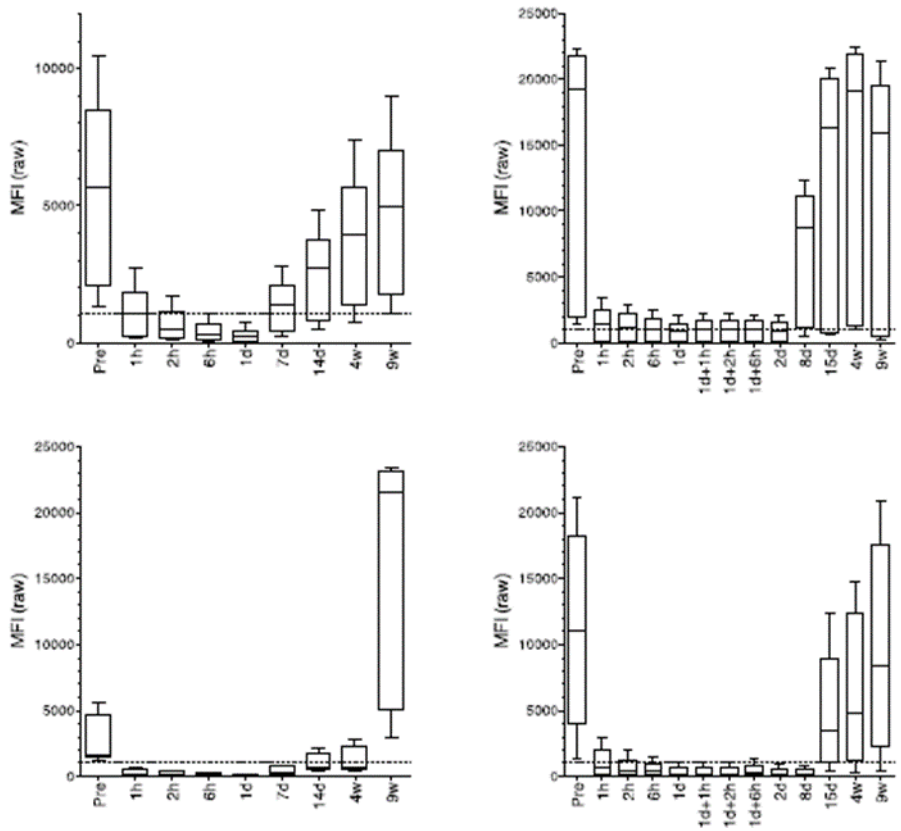
The dosing regimens were investigated for the ability and time frame to completely cleave IgG to its Fc and F(ab')2 fragments.

Eight patients were included in the study and given IdeS infusion (3 males, 5 females; age 31-69 years). One subject was given 0.25 mg/kg, but the infusion was disrupted after about 4 minutes due to infusion reactions.

MFI-measurements at different timepoints post-infusion using the HLA-SAB LabScreen assay for each subject are shown in **Figure 10**. Three patients (group 1) received two doses with 0.12 mg/kg IdeS. Two patients received a single dose of imlifidase at 0.25 mg/kg and two patients received two doses at 0.25 mg/kg (group 2).

**Figure 10 Graphical representation of LabScreen MFI data from HLA having a pre-dose MFI >1,100 (Study 02).**






Horizontal lines represent median MFI, boxes represent the 25th and the 75th percentile and vertical lines represent the 10th and the 90th percentile MFI. The 1100 MFI primary endpoint is indicated with a horizontal dotted line.

The upper 3 graphs present results from group 1 patients and the lower 4 graphs results from group 2 patients.

Compared to group-1, the effect was stronger and more rapid in group-2 treated with 0.25 mg/kg imlifidase. For group-1, there was a clear effect of the second dose that was not seen for group-2.

When applying the LabScreen SAB assay, none of the patients in group-1 but three out of four patients in group-2 reached primary endpoint, whereas when applying the C1qScreen SAB, all HLA had MFI below 1,100 in 5 patient already one hour after Imlifidase treatment ( data were not interpretable for 2 patients due to high background). The discrepancy between the methods is presumed to be due to that single cleaved imlifidase fragments most probably interact with the LabScreen SAB assay.

Results on the ability and time frame to completely cleave IgG to its Fc and F(ab')2 fragments are presented in Section 2.4.3 (**Table 15**, **Table 16**, **Table 17**).

In all patients with significant pre-dose panel reactivity, the percentage PRA was reduced already one hour after imlifidase treatment.

Two subjects were transplanted:

- One subject was transplanted after the second imlifidase dose. Crossmatch was positive for B- and T-cells with both CDCXM and FCXM before imlifidase treatment but six hours after the second dose of imlifidase 0.12 mg/kg, crossmatch was negative, and the subject was transplanted. The applicant clarified that CXMs were performed within the study protocol (without the intent to transplant) based e.g. on a CXM conversion prior to the kidney becoming available for transplantation.

- A second patient was transplanted during the study. However, due to an infusion reaction, this subject received a reduced Imlifidase dose, insufficient for any detectable cleaving of IgG. Furthermore, this subject had PRA 0% at baseline.

***Study 03: A Phase II Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of Intravenous Ascending Doses of IdeS in Kidney Transplantation***

***Methods***

The study was a Phase II, uncontrolled, non-randomised, single ascending dose study performed at two Swedish sites in patients diagnosed with CKD and intended for transplantation. Patients in the first dose group received one IV dose of 0.25 mg/kg IdeS and the second dose group received one dose of 0.50 mg/kg after evaluation of the safety and efficacy in the first group. One or two optional higher dose groups (1.0 mg/kg; 2.0 mg/kg) were planned if needed to achieve sufficient efficacy. The study duration was 180 days.

***Outcomes/endpoints***

Primary Endpoint

- Safety parameters (Adverse events, clinical laboratory tests, vital signs and ECGs)

Secondary Endpoints:

- Efficacy (defined as the IdeS dosing scheme resulting in HLA antibody levels which are acceptable for transplantation, measured as an MFI of less than 1100 as measured in an SAB assay, within 24 hours from dosing); reduction of PRA levels in cytotoxic sera screen after IdeS treatment; result in FACS and cytotoxic crossmatch test after IdeS treatment; PK profile of imlifidase; PD profile of imlifidase (cleavage of IgG); immunogenicity of IdeS by measuring anti-drug antibodies; time to recovery of total serum IgG and HLA-antibody; kidney function; incidence of rejection.

***Results:***

***Participant flow***

A total of 12 patients were screened and 10 patients were enrolled in the study; five patients in the 0.25 mg/kg group (low dose group) and 5 patients in the 0.50 mg/kg group (high dose group). One of the 12 patients was re-screened since more than 28 days passed between the first screening visit and visit 2. Rescreening was allowed according to the protocol if no suitable donor appeared during the first 28 days. All 10 patients enrolled completed the study.

***Baseline data***

Baseline data for all transplanted subjects are given under heading *Analysis performed across trials (pooled analyses and meta-analysis)*.

The mean age was 51.6 years; 70% of the subjects were female and 90% were white. In absolute numbers, the dose groups were comparable regarding gender and race. Mean age was higher in the 0.5 mg/kg than in the 0.25 mg/kg dose group (57.0 vs 46.2 years, respectively). Age is not expected to influence the effect of imlifidase.

**Table 19 Baseline Antibody Status (Study 03)**

| B-cell CDCXM | T-cell CDCXM | B-cell FCXM | T-cell FCXM | Number of DSA[1] |
|---|---|---|---|---|
| *Dose group 0.25 mg/kg* | | | | |
| Negative | Negative | Negative | Negative | 3 |
| Negative | Negative | Negative | Positive | 1 |
| Negative | Negative | Negative | Negative | 1 |
| Negative | Negative | Positive | Negative | 4 |
| Negative | Negative | Negative | Negative | 0 |
| *Dose group 0.50 mg/kg* | | | | |
| Negative | Negative | Negative | Positive | 3 |
| Positive | Negative | Positive | Positive* | 5 |
| Negative | Negative | Positive | Positive | 1 |
| Negative | Negative | Positive | Negative | 1 |
| Negative | Negative | Negative | Negative | 0 |

CDCXM=complement-dependent cytotoxicity crossmatch, DSA=donor-specific antibodies, FCXM=flow cytometry crossmatch

[1]Antibodies against the donor HLA-type with MFI >1100 Baseline defined as visit 2, pre-dose

*Corrected baseline information, that was initially erroneously recorded as 'negative'

***Outcomes and estimation***

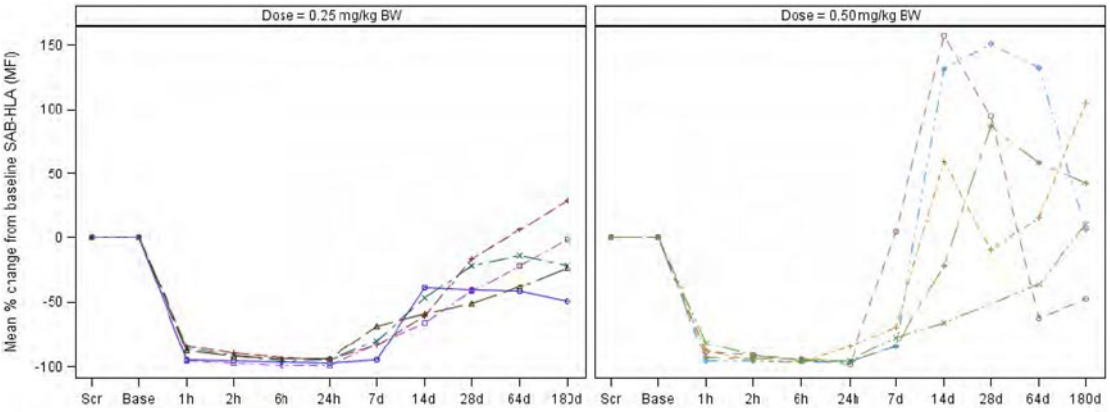
Performance of Transplantation

Patient eligibility for transplantation was assessed by the investigator based on HLA antibody levels and crossmatch tests after IdeS treatment and other factors, such as the expected cold ischaemic time and organ quality. Since no strict criteria for acceptable HLA antibody levels were defined, the performance of the transplantation was regarded as efficacy of imlifidase.

All 10/10 patients were found eligible for transplantation after IdeS treatment and all were transplanted; thus, both imlifidase doses (0.25 mg/kg and 0.50 mg/kg) resulted in HLA antibody levels acceptable for transplantation and negative crossmatch tests.

Individual plots of the mean percentage change from baseline MFI of positive SAB-HLA antibodies are provided in **Figure 11**.

**Figure 11 Mean individual changes from baseline MFI of positive SAB-HLA antibodies – low dose group (left) and high dose group (right) (Study 03)**




The results from C1q-SAB analysis were congruent with the results from the LabScreen anti-HLA SAB analysis.

Donor Specific Antibodies

All individual DSAs in all patients declined rapidly from pre-dose to 1 hour after dosing and remained low until 24 hours in all patients and day 7 in most patients. One subject had a more rapid recovery of DSA. Data on DSA for all transplanted subjects are given under heading *Analysis performed across trials (pooled analyses and meta-analysis)* below.

Conclusions:

Based on the results of Studies 02 and Study 03 a dosing regimen of a 15-minute IV infusion of 0.24/0.25 mg/kg imlifidase was chosen for the subsequent clinical Study 04 and the main Study 06. Since 2×0.25 and 1×0.50 mg/kg had previously been investigated without any safety concerns, there was a possibility to add another dose of 0.24/0.25 mg/kg should the initial dose not be considered sufficient.

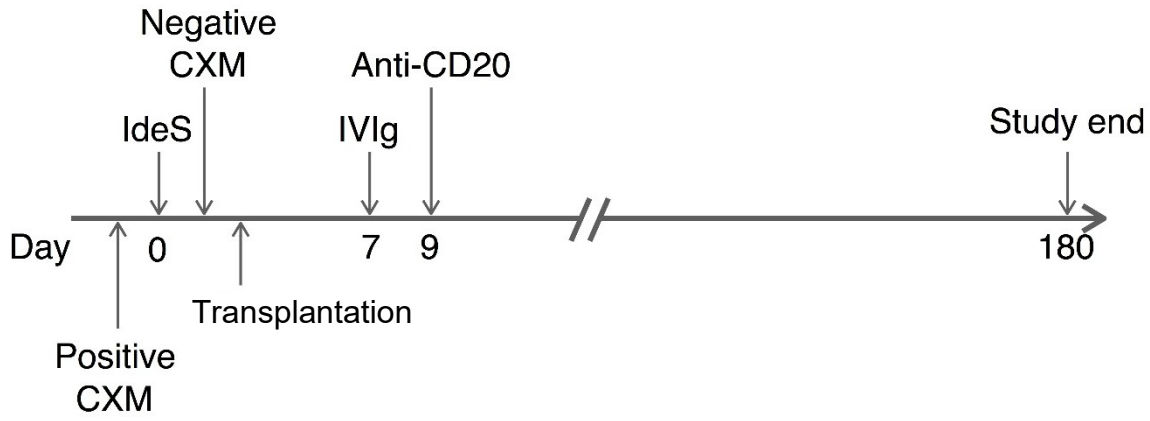
## 2.5.2. Main studies

***Study 06 - A phase II study to evaluate the efficacy of IdeS (IgG endopeptidase) to desensitize transplant patients with a positive crossmatch test***

## *Methods*

Study design is provided in **Figure 12**.

**Figure 12 Overall study design: sequence and timing of study events for each patient**




## *Study Participants*

**Inclusion** criteria:

1. Male or female aged 18-70 years at the time of screening

2. Patients on the kidney transplant waiting list who had previously undergone desensitization unsuccessfully or in whom effective desensitization was highly unlikely. The breadth and strength of sensitisation predict an extremely low likelihood of successful desensitization or kidney paired donation

3. Patients with a live or deceased donor with a positive crossmatch test.

***In Sweden, additionally:***

*a. Fulfil the criteria to be listed on the Scandia Transplant Acceptable Mismatch Program (STAMP):*

*i) On transplantation waiting list >1 year*

*ii) HLA antibody status with PRA ≥80% based on CDC and/or solid phase assay*

*iii) HLA status confirmed by two consecutive samples over a period of more than 3 months*

*iv) Proven reactivity against HLA class I or II antigens or both*

*v) Last tested sample drawn less than 3 months before acceptance*

*b. Patients with a medically acceptable live donor were eligible if they fulfilled the criteria to be listed on the Scandinavian Transplant Kidney Exchange Program (STEP):*

*i) Recipient with DSAs*

*ii) Positive CXM between recipient and live donor*

***In France, additionally:***

*a. DSAs present*

*b. MFI levels of at least 3000*

*2. Patients with a live or deceased (deceased donor not applicable in France) donor with a positive CXM test*

*3. Patients had to be able to understand and sign the informed consent"*

**Main Exclusion** criteria:

1. Previous treatment with imlifidase
2. Previous high dose IVIg treatment (2 g/kg body weight) within 28 days prior to imlifidase treatment
3. Lactating or pregnant females
4. Women of child-bearing age who were not willing or able to practice FDA-approved forms of contraception (**for centres in the USA**) or follow measures laid down in guidelines issued by EMAs Clinical Trial Facilitation Group (CTFG) (2014-09-15) (**for European centres**) as follows:

*a. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation*

*b. Progesterone-only hormonal contraception associated with inhibition of ovulation*

*c. Vasectomised partner, if that partner is the sole sexual partner of the study participant and that the vasectomised partner has received medical assessment of the surgical success*
***In France, additionally**: Men who were not willing to use double-barrier contraception from the first day of treatment until at least 14 days after the last dose of treatment*

5. HIV-positive patients
6. **Sweden and France**: Patients tested positive for HBV infection (positive HBVsAg, HBVcAb, or HBVeAg/DNA) or HCV infection (positive Anti-HCV [EIA] and confirmatory HCV [RIBA]) (within 1 year prior to enrolment for France)

   **USA**: Patients with clinical signs of HBV or HCV infection
7. Patients with active tuberculosis
8. Significantly abnormal general serum screening laboratory result according to the investigator's judgement. Haemoglobin could not be <6.0 g/dL. Laboratory safety results from within 3 days before screening could be used
9. Severe other conditions requiring treatment and close monitoring, e.g. cardiac failure >New York Heart Association grade 3, unstable coronary disease or oxygen dependent chronic obstructive pulmonary disease
10. Individuals deemed unable to comply with the protocol
11. ***Sweden**: Patients with active CMV or EBV infection as defined by CMV-specific serology (IgG or IgM) and confirmed by quantitative PCR with or without a compatible illness*

    ***France**: Patients with active CMV or EBV infection as defined by CMV-specific serology (IgG or IgM) and confirmed by quantitative PCR*

    ***USA**: Patients with clinical signs of CMV or EBV infection*
12. Patients with a history of major thrombotic events, patients with active peripheral vasculardisease or patients with proven hypercoagulable conditions
13. Patients should not have received investigational drugs within 4 half-lives (or similar)

14. Known allergy/sensitivity to any of the ingredients of the IMP
15. Patients who had a live donor and tested positive for ImmunoCAP anti-imlifidase IgE″

## *Treatments*

The Investigational Medicinal Product (IMP) was Imlifidase (a clear colourless liquid formulated at 10 g/L in PBS) and intended for IV administration after dilution. Imlifidase and PBS was supplied by the sponsor.

Imlifidase was administered as an IV infusion over at least 15 minutes using a syringe or an infusion bag, an infusion pump and a particle filter. The patients received one dose of 0.25 mg/kg imlifidase on day 0. If it was considered safe and the desired effect was not achieved (i.e. no CXM test conversion) after the first dose, an additional imlifidase infusion could be given within 2 days of the first infusion.

Prior to imlifidase administration, patients were pre-treated with glucocorticoids and antihistamines.

**In addition to treatment with imlifidase**, patients were treated with high dose IVIg 10% solution 2 g/kg (maximum 140 g for >70 kg) 7 days after imlifidase treatment and 1 g rituximab (anti-CD20 antibody) 9 days after imlifidase treatment, respectively. If deemed necessary by the investigator, the IVIg dose could be split into two doses administered over days 6-8.

**Induction therapy** could be used, if indicated. Sites could use either ATGAM or alemtuzumab. Rabbit ATG could not be used since it is efficiently cleaved by imlifidase. Alemtuzumab could be administered 4 days after imlifidase at the earliest, based on limited experience. If alemtuzumab was used as induction therapy on day 4, pulse steroid treatment could be used up to day 4 to prevent T-cell mediated rejection.

Prophylactic antibiotics were given in all studies to prevent opportunistic infections due to low IgG levels; however, the protocol differed between the studies, e.g. ciprofloxacin was given in Study 04, phenoxymethylpenicillin in study 03 and "according to clinical practice at each site" in Study 06.

## *Objectives*

Primary Objective

- efficacy of imlifidase in creating a negative CXM test

Secondary Objectives

- To determine DSA levels at multiple times (pre-dose, 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180) post imlifidase treatment
- To determine time to creating a negative CDC CXM test (not applicable in France)
- To evaluate safety parameters (AEs, clinical laboratory tests, vital signs and ECGs) following imlifidase treatment up to day 180
- To monitor kidney function after imlifidase treatment as assessed by filtration (eGFR), creatinine and proteinuria
- To establish the PK profile of imlifidase
- To establish the PD profile of imlifidase (cleavage and recovery of IgG)
- To establish the immunogenicity profile of imlifidase (ADA)

### *Outcomes/endpoints*

- Primary Endpoint: efficacy defined as imlifidase ability to create a negative CXM test within 24 hours after imlifidase dosing.
- Secondary Endpoints
    - DSA levels at pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180 post imlifidase treatment
    - Time to creating a negative CDC CXM test (not applicable in France)
    - Time to creating a negative FACS CXM test
    - Safety parameters (AEs, clinical laboratory tests, vital signs and ECGs)
    - Kidney function after imlifidase treatment assessed by, filtration (eGFR), creatinine and proteinuria up to 180 days post treatment
    - PK profile of imlifidase up to day 14
    - PD profile of imlifidase (cleavage and recovery of IgG) up to day 180 post imlifidase
    - Immunogenicity profile of imlifidase by measuring ADA

### *Sample size*

No formal sample size calculation was performed for this study. Due to the nature of the primary endpoint of the study, it was expected that data from 15-20 patients should suffice to achieve the objectives of the study.

### *Randomisation*

The study was single arm, therefore there was no randomisation.

### *Blinding (masking)*

The study was open label, therefore there was no blinding to the study treatment.

### *Statistical methods*

Missing data were not imputed.

### *Results*

## Participant flow

A total of 21 patients were screened and 19 patients enrolled in this study. Of these, 16 patients completed the study and 3 patients were discontinued before the final study visit. Patient disposition including reason for discontinuation is provided in **Table 20**.

**Table 20 Patient disposition including reason for discontinuation**

| | Total N=19 n (%) |
|---|---|
| Screened | 21 |
| Analysis Sets | |
| Safety analysis set (SAS) | 19 (100) |
| Full analysis set (FAS) | 19 (100) |
| Per protocol (PP) analysis set | 18 (95) |
| PK analysis set | 18 (95) |
| Completed | 16 (84) |
| Discontinued | 3 (16) |
| Reason for discontinuation | |
| Adverse event | 1 (5) |
| Protocol deviation | 0 (0) |
| Lost to follow-up | 0 (0) |
| Non-fulfilment of inclusion/exclusion criteria | 0 (0) |
| Withdrawal by patient | 1 (5) |
| Other | 1 (5) |

N=number of patients in FAS; n=number of patients with data

## Recruitment

The study was conducted in 5 centres located in USA, France and Sweden.

First Patient First Visit: 30 September 2016

Last Patient Last Visit: 03 July 2018

## Conduct of the study

The protocol was amended 9 times during the study. Protocol version 3.0 dated 22 April 2016 was the first approved protocol (applicable for the USA).

**Table 21 Clinical study protocols and amendments approved in each participating country**

| France | Sweden | USA |
|---|---|---|
| - | - | Version 3.0 dated 22 Apr 2016 (non-substantial amendment 1. Version not used since no patients were enrolled before version 4.0) |
| Version 4.3 dated 10 Jan 2017 (not used since no patients were enrolled before version 6.2) | Version 4.1 dated 29 Aug 2016 | Version 4.0 dated 29 Aug 2016 (non-substantial amendment 2) |
| Version 6.2 dated 9 May 2017 (substantial amendment 4 and cover letter) | Version 6.1 dated 14 Jun 2017 (substantial amendment 5) | Version 5.0 dated 20 Mar 2017 (substantial amendment 3) |
| Version 7.2 dated 13 Sep 2017 (non-substantial amendment 6) | | |
| Global non-substantial amendment 7 dated 08-Dec-2017 | | |
| Global non-substantial amendment 8 dated 18-Jan-2018 | | |
| Global non-substantial amendment 9 dated 01-Mar-2018 | | |

**Protocol version 4.0 (USA), 4.1 (Sweden), 4.3 (France):** Information about the risk of graft rejection in highly sensitized patients was added to the risk/benefit assessment. The timepoints for assessment of DSAs were corrected in the secondary objectives section 3.2. Patients who were not eligible for transplantation after imlifidase treatment would not be transplanted and thus would not receive any induction therapy or immunosuppression. Patients who received imlifidase would be asked to remain in the study and be followed up according to the study protocol even if they were not transplanted. Patients who lost their graft during the study would remain in the study and be followed up according to the study protocol. The DSMB would continuously monitor the study safety throughout the study and could recommend premature termination of the study if an unacceptable number of serious side effects or graft losses were observed. It was described how investigators, regulatory authorities, IECs/IRBs and patients would be informed in case of premature termination of the study. A section was added describing procedures in case of pregnancies. The procedure for handling of substantial protocol amendments was clarified. A section was added to describe archiving of the investigator study file and the study master file. End of study was defined as the last visit of the last patient.

**Protocol version 4.1 only (Sweden):** Inclusion criterion number 2: country specific criteria to be listed in STAMP or STEP were added. Acceptable contraception according to EMA guidelines were added to exclusion criterion number 4. Exclusion criterion number 14: known allergy/sensitivity to imlifidase infusions was changed to known allergy/sensitivity to any of the ingredients of IMP.

**Protocol version 4.3 only (France):** The possibility of deceased donor transplants was removed; thus, in France the site could start to include living donors after the DSMB had decided to allow living donor patients in the study. The possibility of dose escalation to 0.5 mg/kg was omitted. The time for hospitalisation of patients was increased from 7 to 10 days. The objective and endpoint of time to creating a negative CDC crossmatch test was removed. However, the data granularity did not allow for this endpoint to be calculated for any of the countries. Requirement for DSAs present, a negative CDC CXM test, and a positive FACS CXM test and MFI levels of at least 3000 were added to inclusion criterion number 2. It was added to exclusion criterion number 4 that contraception should be used for 180 days after imlifidase dosing and that men who were not willing to use double-barrier contraception from the first day of treatment until at least 14 days after the last dose of treatment were excluded. All

CDC CXM tests after pre-dose were deleted. A patient would only exit the study if he/she withdrew the consent or was unable to comply with the protocol and that patients who, for a medical reason, could not comply with the protocol procedures would be followed by best procedure to retrieve safety and efficacy data. Rejection episodes or postponed transplantation for any reason would result in the patient leaving the study. A voluntary, precautionary sperm sample prior to imlifidase dosing was added for male patients

**Protocol versions 5.0 (USA), 6.1 (Sweden) and 6.2 (France):** The background was updated with information on a recent study with imlifidase in asymptomatic thrombotic thrombocytopenic purpura patients. Exclusion criterion 12: Patients with a history of clinically significant thrombotic episodes and patients with active peripheral vascular disease was changed to: Patients with a history of major thrombotic events, patients with active peripheral vascular disease or patients with proven hypercoagulable conditions. It was added to the desensitization protocol that the IVIg dose could be split into two doses administrated over days 6-8, if deemed necessary by the investigator, and in such case that PD and ADA samples should be taken before and after the first IVIg dose. The dose of methylprednisolone (250 mg IV) and loratadine (10 mg orally or an equipotent antihistamine) was added to the description of premedication. It was added that the pregnancy test of female patients at screening did not have to be repeated at visit 2 if the patient was hospitalised between screening and visit 2. A kidney biopsy was added at visit 2 on deceased donor kidneys (Sweden and USA only) and at visit 12 on living and deceased donor kidneys (all countries). If standard of care kidney biopsies were performed for any reason, e.g. suspected rejections, a de-identified copy of the kidney biopsy report was collected. The reporting requirements for AEs based on examination and tests was clarified. In the original protocol the wording implied that they should only be reported if they fulfilled any of the SAE criteria or were the reason for discontinuation of treatment with the investigational product. In the updated protocols, it was clarified that they should be reported if laboratory values were judged as clinically significant and/or a treatment had been given for a medical event and if vital signs resulted in clinical signs/symptoms and/or required treatment. It was clarified that the Safety Management Plan was an agreement between the sponsor and Drug Safety Navigator. The timelines for pregnancy reporting was changed from 2 weeks to 24 hours

**Protocol version 5.0 only (USA):** Exclusion criterion number 6: Patients who test positive for HBV infection (positive HBVsAg, HBVcAb, or HBVeAg/DNA) or HCV infection (positive Anti-HCV [EIA] and confirmatory HCV [RIBA]) was changed to: Patients with clinical signs of HBV or HCV infection. Exclusion criterion number 11: Patients with active CMV or EBV infection as defined by CMV-specific serology (IgG or IgM) and confirmed by quantitative PCR with or without a compatible illness was changed to: Patients with clinical signs of CMV or EBV infection. It was added that previous test results, not older than 6 months, for HIV, hepatitis, BK, EBV, CMV could be used for screening

**Protocol version 6.1 (Sweden):** It was added that a negative virus serology performed within 6 months before the screening visit was accepted for enrolment, but that virus serology would still be performed at the screening visit. It was added that a specialist in infectious diseases would be part of the transplantation team and available for medical advice and evaluation of the patient in case of infection/viral reactivation during the study. Treatment for infection/viral reactivation was initiated based on the recommendations for the individual patient. In case of reactivation of hepatitis B, rituximab was not administered to the patient

**Protocol version 6.2 only (France):** "Within one year prior to enrolment" was added to exclusion criterion number 6 regarding positive test for HBV or HCV infection. "With or without a compatible illness" was deleted from exclusion criterion number 11. It was added that previous test results, not older than 6 months, for HIV, hepatitis, BK, EBV, CMV could be used for screening

**Protocol version 7.2 for France**

• The country-specific requirement for a negative CDC CXM test and a positive FACS CXM test was deleted for inclusion criterion 2. By error, the flowchart in the protocol was not updated to include CDC CXM tests after dosing; however, the CDC CXM tests were described in the protocol section 6.5 and performed as intended.

**Global non-substantial amendment number 7:** The following additional retrospective data for donors and patients were collected to support evaluation of kidney function and treatment of sensitized patients before and after kidney transplantation. Demographics and medical history of donor and details of donor organ. Extended data on the patients' medical history (kidney). Additional details on CXM tests, delayed graft function and graft rejection episodes

**Global non-substantial amendment number 8:** Determination of IgG in serum (PD) was not performed at visit 12 (day 180). The PD analysis differentiates between scIgG and intact IgG, and since scIgG is only present in serum for 2-3 weeks after imlifidase treatment, the analysis would add not value to the study. Safety laboratory IgG analysed at the local laboratories was still performed.

**Global non-substantial amendment number 9:** DSAs were analysed in serum at an additional timepoint 96 hours after imlifidase treatment since it was discovered it would be beneficial for the interpretation of the effect of imlifidase on DSAs. No additional blood sample was necessary, since a PK sample was collected per protocol at this timepoint.

## Baseline data

A summary of demographics and body measurements for Study 06 is shown in **Table 22**. Of the 19 enrolled patients, 6 patients were females and 13 were males. The mean (SD) age was 39.1 (10.8) years and the mean (SD) BMI was 24.6 (4.5) kg/$m^2$.

**Table 22 Demographic and baseline characteristics**

| | | **Total N=19** |
|---|---|---|
| Age (years) | Mean (SD) | 39.1 (10.8) |
| | Median | 40 |
| | Min; max | 20; 64 |
| Sex, n (%) | Female | 6 (32) |
| | Male | 13 (68) |
| Race, n (%) | Asian | 1 (5) |
| | Black or African American | 4 (21) |
| | White | 12 (63) |
| | Other | 2 (11) |
| Weight (kg) | Mean (SD) | 73.2 (15.7) |
| | Median | 71.6 |
| | Min; max | 45.1; 107.4 |
| BMI (kg/$m^2$) | Mean (SD) | 24.6 (4.5) |
| | Median | 24.3 |
| | Min; max | 17.5; 32.5 |

N=number of patients in SAS; SD=standard deviation; %, percentage of patients in SAS

**Table 23** summarises the results of the pre-dose CXM tests by type of test. All patients had at least one positive CXM test at pre-dose.

**Table 23 Summary of pre-dose CXM results by type of test**

| Response | FACS-B N=19 n (%) | FACS-T N=19 n (%) | CDC-B N=19 n (%) | CDC-T N=19 n (%) | Virtual N=19 n (%) |
|---|---|---|---|---|---|
| Positive | 18 (94.7%) | 7 (36.8%) | 8 (42.1%) | 2 (10.5%) | 5 (26.3%) |
| Negative | 0 | 12 (63.2%) | 2 (10.5%) | 11 (57.9%) | 0 |
| Not determined | 1 (5.3%) | 0 | 9 (47.4%) | 6 (31.6%) | 14 (73.7%) |

N=number of patients in FAS; n=number of patients; %=percentage of patients in FAS

All patients had positive HLA antibodies (defined as SAB-HLA antibodies with MFI >3000) at baseline. After a 10 times dilution, the median MFI for the positive HLA antibodies was still >3000 MFI for 10 patients, and for 3 patients the median MFI level was still >3000 after a 100 times dilution.

After a 100 times dilution, maximum MFI values >3000 were seen for 14 of the patients and for 9 of these patients, the maximum MFI values were >17000.

Most of the patients were highly sensitized (defined as a cPRA above 80%). **Table 24** shows the cPRA at different MFI cut-off levels. At 2000 MFI, 16 patients had cPRA above 80%, 13 patients had cPRA above 95% and 11 patients had cPRA of 100%.

**Table 24 cPRA at different MFI cut-off levels (FAS)**

| | **Unacceptable levels (MFI)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **cPRA (%)** | **500 N=18 n (%)** | **1000 N=18 n (%)** | **2000 N=18 n (%)** | **3000 N=18 n (%)** | **5000 N=18 n (%)** | **7500 N=18 n (%)** | **10000 N=18 n (%)** | **15000 N=18 n (%)** | **20000 N=18 n (%)** |
| Under 80% | 2 (11.1) | 2 (11.1) | 2 (11.1) | 2 (11.1) | 4 (22.2) | 5 (27.8) | 5 (27.8) | 6 (33.3) | 12 (66.7) |
| 80-95% | 0 | 0 | 3 (16.7) | 3 (16.7) | 1 (5.6) | 1 (5.6) | 3 (16.7) | 6 (33.3) | 5 (27.8) |
| 95-98% | 0 | 1 (5.6) | 0 | 1 (5.6) | 1 (5.6) | 4 (22.2) | 3 (16.7) | 3 (16.7) | 1 (5.6) |
| 98% (97.51-98.50) | 1 (5.6) | 3 (16.7) | 1 (5.6) | 0 | 1 (5.6) | | 0 | 1 (5.6) | 0 |
| 99% (98.51-99.50) | 2 (11.1) | 1 (5.6) | 1 (5.6) | 5 (27.8) | 7 (38.9) | 5 (27.8) | 5 (27.8) | 2 (11.1) | 0 |
| 100% (99.51 - 100) | 13 (72.2) | 11 (61.1) | 11 (61.1) | 7 (38.9) | 4 (22.2) | 3 (16.7) | 2 (11.1) | 0 | 0 |

N=number of patients in FAS with data; n=number of patients; %=percentage of patients with data
One patient did not have any HLA data for cPRA calculation
Analysis performed on undiluted pre-dose serum samples

***Extent of exposure***

19 patients were exposed to imlifidase in this study; 15 patients received 1 dose of 0.25 mg/kg, 3 patients) received 2 doses of 0.25 mg/kg and 1 patient) received a total dose of approximately 4 mg corresponding to 0.058 mg/kg.

Treatment compliance was assessed by comparison of the planned dose with the actual dose administered. Of the 19 patients exposed, 18 patients received the planned dose and had 100% compliance, while 1 patient) received less than 25% of the planned dose due to an infusion related reaction that resulted in withdrawal of study drug. In 2 patients, the infusion was interrupted temporarily but continued after 12 and 18 minutes, respectively, due to AEs. Both patients received a full dose of imlifidase.

## Numbers analysed

Nineteen patients were in the SAS, 19 patients were in the FAS, of whom 18 were transplanted.

Of the 18 patients transplanted, 13 patients received a kidney from a deceased donor and 5 patients received a kidney from a living donor. For the living donor transplants, 2 patients received a donor from a relative and 3 patients were unrelated to the donor. The cold ischaemia time for deceased donor transplants ranged from approximately 9 hours to 46 hours.

For 2 patients, the blood type of the recipient was not identical to the donor blood type; however, all transplants were ABO compatible.

**Rejection medication**
Half of the transplanted patients (9 patients) were treated for graft rejection on one or more occasion between day 4 and day 142 after transplantation. The most commonly used treatments were immunoglobulins (12 events in 4 patients), selective immunosuppressants (11 events in 3 patients), PLEX (9 events in 6 patients) and glucocorticoids (5 events in 5 patients).

## Outcomes and estimation

***Primary Endpoint***

The primary endpoint was the ability of imlifidase to convert a positive CXM to a negative within 24 hours after dosing. For each patient, the primary endpoint was met if at least one assay was positive at pre-dose and the last assay within 24 hours post-dose was negative.

Of the 19 patients in the FAS, 17 patients (89.5%) were converted from a positive to a negative CXM, while 2 patients (10.5% of the FAS) were not converted (**Table 25**).

**Table 25 Summary of CXM response (FAS)**

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

One patient, , had a positive FACS T-cell CXM test 24 hours after dosing. One patient, , received less than 25% of the planned dose due to an infusion reaction resulting in withdrawal of study drug.

***Secondary (Efficacy) Endpoints***

**Donor specific antibodies (DSA)**

All patients had at least 1 HLA mismatch at baseline with the highest number of mismatches for an individual patient being 12.

Of the 18 patients who had available HLA data and were transplanted, 17 patients had at least 1 DSA with MFI value >3000 at pre-dose. After dosing, DSAs declined rapidly and for 11 patients, all were <3000, 2 hours after dosing. For the remaining 7 patients, all DSAs reached an MFI level <3000 at 6 hours after dosing (4 patients), hour 48 (1 patient), hour 96 (1 patient), and day 90 (1 patient).

**Time to negative CDC and FACS CXM tests**

Due to many missing values for the CXM tests at timepoints between pre-dose and 24 hours, the time to a negative CXM test could not be calculated.

**Kidney function**

Data on renal function are provided in **Table 26**.

**Table 26 Kidney function by patient on days 28, 90 and 180**

| Creatinine (µmol/L) | | | eGFR (mL/min/1.73 $m^2$) | | | Proteinuria (dipstick) | | |
|---|---|---|---|---|---|---|---|---|
| Day 28 | Day 90 | Day 180 | Day 28 | Day 90 | Day 180 | Day 28 | Day 90 | Day 180 |
| 743 | -[a] | -[a] | 8.2 | -[a] | -[a] | - | -[a] | -[a] |
| 522 | 522 | -[c] | 10.7 | 10.7 | 10.5[b,c] | - | Positive | Positive[b,c] |
| 133 | 124 | - | 49.0 | 53.0 | 57.7[b] | Negative | Positive | Positive[b] |
| 150 | 97[d] | 88[d] | 31.9 | 52.8 | 58.9 | Negative | Negative | Negative |
| 133 | 97[d] | 141 | 50.8 | 72.7 | 47.2 | Positive | Positive | Negative |
| 124 | 124 | 124 | 56.1 | 56.1 | 56.1 | Positive | Positive | Positive |
| 115[d] | 97[d] | 106[d] | 55.6 | 67.4 | 61.0 | Positive | Positive | Positive |
| 460 | 283 | 159 | 10.8 | 19.0 | 36.9 | Positive | Positive | Positive |
| 469 | 292 | 309 | 12.7 | 22.0 | 20.5 | Positive | Positive | Positive |
| 248 | 221 | 248 | 30.6 | 34.8 | 30.6 | Positive | Positive | Positive |
| 97 | 88[d] | 71[d] | 57.9 | 64.7 | 83.7 | Positive | Positive | Positive |
| 141 | 133 | 190 | 50.0 | 53.9 | 35.6 | Positive | Positive | Positive |
| 80[d] | 95 | 91 | 83.2 | 67.4 | 71.2 | Positive | Positive | Positive |
| 133 | 181 | 201 | 63.1 | 44.0 | 39.1 | Positive | Positive | Positive |
| 127 | 143 | 120 | 39.5 | 34.4 | 42.1 | Negative | Negative | Negative |
| 109 | 96[d] | 79[d] | 63.5 | 73.5 | 92.0 | Negative | Negative | Negative |
| 503 | 234 | 199 | 11.4 | 27.7 | 33.3 | - | - | - |
| 115 | 127 | 144 | 68.4 | 61.0 | 52.7 | - | - | - |

## *Supportive study*

***Study 04 - Phase I/II Trial to Evaluate the Safety and Tolerability of IdeS (IgG endopeptidase) to Eliminate Donor Specific HLA Antibodies (DSAs) and Prevent Antibody Mediated Rejection Post-Transplant in Highly-HLA Sensitized Patients (considered as a main supportive study)***

## *Methods*

Study 04 was an uncontrolled single centre, phase I/II, open label exploratory study. Study design is provided in **Table 27**.

**Table 27 Overall trial design: sequence and timing of trial events for each subject**

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

## *Study participants*

Inclusion criteria:

- End-stage renal disease awaiting transplantation on the UNOS list.
- No known contraindications for therapy with IVIg 10%, Rituximab, plasmapheresis (PLEX) or imlifidase.
- Age 18-70 years at the time of screening.
- cPRA >50% demonstrated on 3 consecutive samples, patient highly-HLA sensitized and a candidate for DD kidney transplantation after desensitization.
- At transplantation, the patient must have a donor-specific antibody/ crossmatch positive (DSA/CMX+) non-HLA identical donor.
- Pre-transplant vaccination with *Streptococcus pneumoniae* and *Nisseria meningitides*
- Able to understand and provide informed consent.

Exclusion criteria:

- Positivity for anti-imlifidase IgE *(this criterion was removed by amendment Ame 18156))*
- Use of IVIg within 7 days prior to planned imlifidase administration (*changed from 4 weeks by amendment Ame 16803*)
- Recipients of kidneys from Extended Criteria Donors (ECD) or Living Donors (LD)
- Lactating or pregnant females.
- Women of child-bearing age who were not willing or able to practice FDA-approved forms of contraception.
- HIV-positive subjects.
- Positive test for HBV infection [positive HBsAg, anti-HBcAb, or HBVeAg/DNA] or HCV infection [positive Anti-HCV (EIA) and confirmatory HCV RIBA].
- Active tuberculosis.
- Selective IgA deficiency, those who have known anti-IgA antibodies, and those with a history of anaphylaxis or severe systemic responses to any part of the clinical trial material.
- Subjects who have received or for whom multiple organ transplants were planned.
- Recent vaccination with any licensed or investigational live attenuated vaccine(s) within two months of the screening visit

- A significantly abnormal general serum screening lab result defined as a WBC <3.0 X $10^3$/mL, a Hgb <8.0 g/dL, a platelet count <100 X $10^3$/mL, an aspartate aminotransferase
  >3X upper limit.
- Individuals deemed unable to comply with the protocol.
- Subjects with active CMV or EBV infection as defined by CMV-specific serology (IgG or IgM) and confirmed by quantitative PCR with or without a compatible illness.
- Subjects with a known history of previous myocardial infarction within one year of screening.
- Subjects with a history of clinically significant thrombotic episodes, and subjects with active peripheral vascular disease.
- Subjects with Protein C and Protein S deficiency
- Use of investigational agents within 4 weeks of participation.
- Known allergy/sensitivity to imlifidase infusions

## *Treatments*

The subjects received one dose of imlifidase, 0.24 mg/kg, 4-6 h before transplantation.

The patients received prophylactic antibiotics (ciprofloxacin).

Regardless of the CMV status, patients received viral prophylaxis for 6 months. Fungal prophylaxis was given for 1 month and prophylaxis against *Pneumocystis jirovecii* pneumonia for 12 months.

Induction treatment with alemtuzumab was given 4 days post-transplant. In addition, high dose corticosteroids were administered on Days 1-4.

Imlifidase was given in addition to the standard post-transplant immunosuppressive protocol

High dose Intravenous immunoglobulin (IVIg) (2 g/kg) was administered on Days 14-21 to 14 patients or 7-14 to 3 patients after transplantation.

## *Objectives*

Primary objectives

- Efficacy of imlifidase in eliminating DSAs in DSA- and flow cytometry CMX positive, highly sensitized patients
- Safety of imlifidase
- Limited assessments of transplantation efficacy and kidney function

Secondary objectives

- Assess if imlifidase can prevent or significantly reduce (from 25% to 5%) AMR episodes and C4d deposition in HLA-incompatible renal transplantation to highly sensitised patients
- Assess allograft function up to 6 months post-transplant

## *Outcomes/endpoints*

Primary Endpoints

- Number and levels of DSAs prior to transplantation
- Number and levels of DSA levels post transplantation
- Incidence of allograft rejections
- Renal function by creatinine, eGFR, and urine protein measurements
- Biopsy pathology evaluation
- Safety parameters (AEs, laboratory assessments, vital signs, ECG)

Secondary Endpoints

- Incidence of AMR findings at end of study (protocol biopsies)
- Incidence of C4d depositions
- Long-term allograft function (S-creatinine and eGFR)

## *Sample size*

No formal sample size calculation was performed for this study.

## *Randomisation*

The study was single arm, therefore there was no randomisation.

## *Blinding (masking)*

The study was open label, therefore there was no blinding to the study treatment.

## *Statistical methods*

Descriptive

## *Results*

## *Participant flow*

27 subjects were screened, and 17 subjects were dosed. No information on screen failure was provided.

All dosed subjects received 0.24 mg/kg imlifidase.

**Table 28 Subject disposition**

| | **Total N=17** |
|---|---|
| | **N (%)** |
| Full analysis set | 17 (100) |
| Safety analysis set | 17 (100) |
| Completed | 15 (88) |
| Discontinued | 2 (12) |
| Withdrawal by subject | 1 (6) |
| Lost to follow-up | 1 (6) |

## Recruitment

The study was conducted in one centre located in USA.

First Patient First Visit: 16 June 2015

Last Patient Last Visit: 03 June 2017

## Conduct of the study

Four amendments to the original protocol were introduced

Amendment 1, Ame 15807, dated 20 May 2015, introduced the following changes:

- Change in personnel
- Change in frequency of collection of DSA, safety laboratory samples, and anti-imlifidase antibodies

Amendment 2, Ame 16803, dated 22 October 2015, introducing the following changes:

- Change in personnel
- Screening of anti-imlifidase antibodies was omitted
- Use of IVIg was allowed up to 7 days prior to imlifidase treatment
- Subjects testing positive for HBV and HCV DNA and/or RNA PCR were excluded
- Addition of serum IgG to standard of care

Amendment 3, Ame 18156, dated 7 June 2016, introduced the following changes:

- Change in personnel
- Requirement of test for negative anti-imlifidase IgE was cancelled
- The intended increase in dose to 0.50 mg/kg for the last 10 patients was cancelled
- Clarification that imlifidase should be dosed a minimum of 4-6 hours prior to transplantation
- IVIg should be administered from Day 7 after transplantation instead of from Day 14

Non-substantial amendment dated 8 December 2017 introduced the following changes:

- Complementary information on demographics were collected
- Additional analyses of DSA at 2 hours, and on Days 2, 3, 4, 7, and 14 from existing samples

## *Baseline data*

Baseline demographics are summarised in **Table 29**. The mean age in Study 04 was 41.3 years. 53% were female and 82% were white.

**Table 29 Demographics (FAS) (Study 04)**

| | | Total N=17 |
|---|---|---|
| | | n (%) |
| Sex | Female n (%) Male n (%) | 9 (53%) 8 (47%) |
| Age [years] | Mean (SD)<br>Median<br>Range | 41.3 (13.3)<br>41<br>20-63 |
| Weight [kg] | Mean (SD)<br>Median<br>Range | 65.5 (18.0)<br>68.8<br>31.3-94.6 |
| BMI | Mean (SD)<br>Median<br>Range | 24.4 (5.5)<br>24.3<br>13.5-36.6 |

N=number of patients; SD=standard deviation; Min=minimum; Max=maximum.

All except three subjects were of Caucasian origin (Asian [2], other [1]).

*Baseline antibody status*

Pre-dose DSAs are summarised in **Table 30**.

**Table 30 Number of identified DSAs and DSAs with MFI value >2,000 (Study 04)**

| Subject No. | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| All DSAs | 6 | 11 | 10 | 9 | 7 | 7 | 9 | 12 | 1 | 9 | 7 | 4 | 5 | 9 | 7 | 9 | 8 |
| DSAs with MFI >2000 | 4 | 2 | 0 | 3 | 2 | 1 | 1 | 2 | 0 | 1 | 1 | 2 | 1 | 5 | 2 | 3 | 3 |

Six of the subjects were positive on both B-cell and T-cell FCXM while three subjects were negative in both (**Table 31**).

**Table 31 Number of patients with positive and/or negative B- and T-cell FCXM test prior to imlifidase infusion (Study 04)**

| | Positive T-cell FCXM<br>N=17 | Negative T-cell FCXM<br>N=17 |
|---|---|---|
| | n (%) | n (%) |
| Positive B-cell cross-match | 6 (35) | 8 (47) |
| Negative B-cell cross-match | 0 (0) | 3 (18) |

There were 3 violations of the inclusion criterion No. 4 ("cPRA >50% demonstrated on 3 consecutive samples, patient highly-HLA sensitized and a candidate for DD kidney transplantation after desensitization") by not being desensitized with IVIg and rituximab prior to being enrolled in the study. However, the Investigator regarded the deviation as minor, not affecting data interpretation, and the patients were therefore included.

Two subjects did not fulfil the requirement of an MFI value >2,000 for any DSA. One of them had 2 DSAs with MFI values of 1,888 and 1,711.

Two subjects who did not fulfil the requirement of an MFI value >2,000 for any DSA pre-treatment were also among the three subjects with negative B- and T-cell FCXM at baseline. Even though these subjects are highly sensitised (cPRA 87.9% and 99.6% at MFI >2,000).

At an MFI cut-off of 2,000 all subjects had a cPRA >80% and increasing the accepted MFI level to 3,000 changed 1 subject to <80% (79%).

## Numbers analysed

All 17 enrolled subjects were included in the full analysis set (FAS), Safety analysis set (SAS) and per-protocol population (PP).

## Outcomes and estimation

***Primary endpoint***

DSA

Six hours after administration all DSAs for all but one subject showed MFI values <2,000. This subject had six DSAs ranging from 317 to 21,971 in MFI level (median 11,835) before treatment.

Allograft rejections

One subject (1/17; 5.9%) suffered a hyperacute antibody-mediated rejection of the kidney with graft loss.

Renal function

Renal function was assessed as serum creatinine/eGFR (**Table 32**) and analysis of proteinuria (**Table 33**).

**Table 32 Summary of renal function**

| Time | | Creatinine, mmol/L N=17 | eGFR mg/mL/1.73 $m^2$ N=17 |
|---|---|---|---|
| Predose | n | 12 | 12 |
| | Mean (SD) | 941 (352) | 5.9 (4.6) |
| | Median Min; max | 858 | 4.8 |
| | | 230 ; 1520 | 2.8 ; 19.8 |
| Day 7 | n | 15 | 15 |
| | Mean (SD) | 393 (278) | 25.0 (22.2) |
| | Median | 327 | 16.7 |
| | Min; max | 80 ; 919 | 4.2 ; 69.7 |
| Day 14 | n | 16 | 16 |
| | Mean (SD) | 256 (210) | 41.4 (47.4) |
| | Median | 208 | 22.6 |
| | Min; max | 35 ; 919 | 6.2 ; 204 |
| Day 21 | n | 16 | 16 |
| | Mean (SD) | 170 (127) | 49.0 (34.1) |
| | Median Min; max | 146 | 40.2 |
| | | 44 ; 592 | 10.2 ; 157 |
| Day 30 | n | 15 | 15 |
| | Mean (SD) | 157 (147) | 64.4 (64.1) |
| | Median Min; max | 141 | 47.9 |
| | | 27 ; 654 | 9.1 ; 284 |
| Day 90 | n | 16 | 16 |
| | Mean (SD) | 125 (88) | 65.9 (42.1) |
| | Median Min; max | 111 | 54.6 |
| | | 35 ; 415 | 15.4 ; 204 |
| Day 180 | n | 12 | 12 |
| | Mean (SD) | 106 (57) | 75.1 (46.7) |
| | Median Min; max | 80 | 67.2 |
| | | 35 ; 239 | 29.2 ; 204 |

**Table 33 Presence of proteinuria**

| Time | Proteinuria category N=16 | | | |
|---|---|---|---|---|
| | Negative n (%) | 1+ n (%) | 2+ n (%) | 3+ n (%) |
| Day 7; N=13 | 3 (31) | 8[1] (54) | 2 (15) | - |
| Day 14; N=15 | 7 (47) | 7 (47) | 1 (7) | - |
| Day 21; N=15 | 11 (73) | 3 (20) | 1 (7) | - |
| Day 30; N=16 | 13 (81) | 1 (6) | 2 (13) | - |
| Day 90; N=16 | 13 (81) | 2 (13) | 1 (6) | - |
| Day 180; N=13 | 10 (77) | - | 2 (15) | 1 (8) |

Antibody mediated rejections

**Table 34 Patients with biopsy confirmed subclinical or acute/active ABMR and/or CMR reported as an AE/SAE**

| Subject No | Diagnosis | Day of biopsy | Reason for biopsy | AE/SAE | DSA Yes/No | eGFR mL/min/1.73m2 | Hansa judgement |
|---|---|---|---|---|---|---|---|
| | Suspicious. ABMR and CMR | 157 | Protocol | SAE | Yes | 20; no change over time | Active ABMR and CMR |
| | Acute CMR | 6 | Rejection episode | SAE | No | 42 | Acute CMR |
| | Suggested ABMR and CMR | 198 | Protocol | SAE | No | >60 | Acute CMR |
| | CMR | 161 | Protocol | AE | No | Day 180:>60 | CMR |
| | Suspicious. ABMR and CMR | 70 | Rejection episode | SAE | No | Day 30: 30<br>Day 90: 34 | Borderline CMR |
| | Borderline CMR | 159 | Rejection episode | AE | No | Day 180: 43 | Borderline CMR |
| | ABMR and CMR | 51 | Slow graft function | SAE | No | Day 36: 42<br>Day 90: 48 | CMR |
| | ABMR and CMR | 70 | Rejection, oliguria | SAE | Yes | Day 30: >60<br>Day 90: 47 | Chronic ABMR and CMR |
| | HAR | 2 | Hyper-acute rejection | SAE | No | NA | Hyperacute rejection IgM mediated |
| | CMR | 49 | suboptimal creatinine | SAE | Yes (Day 14) | Day 30: 29<br>Day 90: 31 | CMR |

***Secondary endpoint:***

Per protocol kidney biopsies at the end of study

Signs of active AMR were observed in 1 (6%) subject, and signs of AMR characterised by biopsy findings and presence of DSA but without clinical signs of ongoing deterioration of the kidney function was observed in 1 (6%) subject, and therefore defined as subclinical AMR. In another two subjects, signs of AMR were seen in the absence of DSA.

C4d depositions

None of the subjects showed any C4d depositions as assessed by the biopsy analyses.

## Summary of main study

The following table summarises the efficacy results from the main study supporting the present application.

**Table 35 Summary of Efficacy for trial 06**

| | | | |
|---|---|---|---|
| **Title:** A phase II study to evaluate the efficacy of IdeS (IgG endopeptidase) to desensitize transplant patients with a positive crossmatch test | | | |
| Study identifier | 15-HMedIdeS-06<br>EudraCT Number: 2016-002064-13<br>IND Number: 128074 | | |
| Design | An open label, single arm (not randomized, not stratified), multicentre, multinational (up to global), dose-escalation, fixed-dose response trial | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 180 days<br>Not applicable<br>Currently not applicable |
| Hypothesis | None | | |
| Treatments groups | Patients on the kidney transplant waitlist with a live or deceased donor with a positive CXM test | | 19 Patients receiving 1 to 2 treatments of 0.25 mg/kg imlifidase |
| Endpoints and definitions | Primary endpoint (CMX con-version) | ability (of imlifidase) to create a negative CXM test within 24 hours after imlifidase dosing. | "a" CMX may refer to one of overall 7 cross-match tests - namely FACS T, FACS B, amplified CDC T, amplified CDC B, not-amplified CDC T, not-amplified CDC B, and virtual CXM |

| | | | |
|---|---|---|---|
| | Secondary endpoint | DSA levels at pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180 post imlifidase treatment | Intended to be descriptively analysed |
| | Secondary endpoint | Time to creating a negative CDC CXM test (not applicable in France)<br>• Time to creating a negative FACS CXM test | Intended to be descriptively analysed |
| Database lock | Mentioned but date not provided in the CSR | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Per protocol<br>Database lock date not specified, date of the CSR<br>CSR date on 29 November 2018<br>First Patient First Visit (CSR): 30 September 2016<br>Last Patient Last Visit (CSR): 03 July 2018 | | |
| Effect estimate per comparison | Primary endpoint (any CMX conversion) | Comparison groups<br>N/A | CKD |
| | | Ratio Yes/No | 17/19= 89.5% |
| | | variability statistic | N/A |
| | | P-value | N/A |
| | Secondary endpoint (time course of DSAs) | Comparison groups<br>N/A | CKD |
| | | test statistic: description of shifts over time of 1 to 12 DSAs (per single patient) | DSA MFI values <2,000<br>Predose: 0/18 (0%)<br>1h: 8/18 (44%)<br>6h: 11/18 (61%)<br>24h: 14/18 (78%) |

| | | | |
|---|---|---|---|
| | | variability statistic | N/A |
| | | P-value | N/A |
| | Time to any CDC and FACS CMX conversion | Comparison groups N/A | CKD |
| | | test statistic | No test conducted and reported |
| | | variability statistic | Not reported |
| | | P-value | Not reported |
| Notes | | | |
| **Analysis description** | **Secondary analysis, Co-primary Analysis** | | |
| | None performed | | |

## Analysis performed across trials (pooled analyses and meta-analysis)

In total, 54 subjects were enrolled and treated with imlifidase in the clinical programme (Study 02, study 03, Study 04 and Study 06). Patients from studies 02 and 03 were retrospectively followed up in study 13.

All transplanted subjects received 0.25 or 0.5 mg/kg imlifidase.

The pooled analysis comprises 46 patients:

- 45 transplanted patients following imlifidase treatment from Studies 03, 04 and 06 where transplantation was part of the study protocol. One subject from Study 06 is excluded since they did not receive a transplant due to an AE during imlifidase infusion.
- One subject from Study 02, where transplantation was not part of the protocol, was transplanted after imlifidase treatment and is therefore included in the pooled analysis. A second subject in Study 02 received a renal transplant in the study, however, this patient is excluded from the pooled analysis since the imlifidase infusion was interrupted due to an infusion reaction.

Study population – transplanted subjects

38 of the 46 transplanted patients are regarded by the applicant as being highly unlikely to have been transplanted without imlifidase treatment, based on the cPRA, presence of DSA and crossmatch, and history of unsuccessful transplantations. The patients were on the kidney transplant waiting list and had previously undergone unsuccessful desensitization, or effective desensitization was highly unlikely. The earlier study 02 and study 03 did not specifically target patients highly unlikely to receive a compatible kidney. However, 3 of the 11 transplanted patients in these studies are, according to the applicant, regarded as qualifying in this category due to very high PRA levels.

Baseline demographics for all transplanted subjects are summarised in **Table 36**.

**Table 36 Demographics and baseline characteristics of transplanted patients**

| Characteristics | Study 02<br>N=1 | Study 03<br>N=10 | Study 04<br>N=17 | Study 06<br>N=18 | All<br>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 >2000)** | | | | | |
| Median | 42 | 71.8 | 98.6 | 99.6 | 98.4 |
| **Living donor** | 0 | 2 | 0 | 5 | 7 |
| **Deceased donor** | 1 | 8 | 17 | 13 | 39 |
| **Previous attempts of desensitization (n)** | 0 | 0 | 14 | 5 | 19 |

Study 02 and Study 03 were conducted in Sweden, where desensitization programs do not currently exist

cPRA: Anti-HLA analysed by central reading by Hansa Biopharma AB, Lund. SWE. Calculated using the cPRA calculator hosted by OPTN (UNetSM computer system) (cut-off >2,000 MFI)

In **Table 37**, the transplanted patients are categorized based on their highest pre-dose MFI value for a DSA.

**Table 37 Number of patients with the highest pre-dose MFI value for a DSA**

| MFI of highest DSA, pre-dose | All transplanted patients N=46 | Highly unlikely to be transplanted N=38 |
|---|---|---|
| | n (%) | n (%) |
| **<1000** | 3 (7) | 1 (2) |
| **1000-3000** | 5 (11) | 4 (11) |
| **3000-6000** | 14 (30) | 11 (29) |
| **6000-9000** | 5 (11) | 4 (11) |
| **9000-12000** | 6 (13) | 5 (13) |
| **>12000** | 13 (28) | 13 (34) |

38/46 transplanted subjects (83%) had a highest pre-dose MFI value for a DSA ≥3,000 which is considered a contraindication for transplantation with that specific donor at most transplantation centers.

cPRA is an important calculated measure that translates into a patient's ability to receive a transplant within a reasonable time frame. The median cPRA, which compares a patient's profile of unacceptable HLA antibodies against >12,000 US donors, was 99.53% (cut-off MFI value 2,000) among the 38 patients highly unlikely to be transplanted, with 22 patients having a cPRA >99.00%, and 10 patients having a cPRA ≥99.95% (i.e. 100.0%). From using the median cPRA to simulate the likelihood of each of these patients being offered a kidney transplant from a compatible donor, it was concluded that 17 (45%) patients had 0.000%, 21 (55%) had <0.030% and 33 (87%) had <0.075% compatible donors in the Eurotransplant database.

*Crossmatch conversion*

Results from crossmatch analyses by study are summarised in **Table 38**. 39/46 (85%) transplanted subjects had a positive crossmatch before imlifidase treatment.

In Study 04, crossmatch conversion was not an endpoint, thus post-dose crossmatch analyses were not performed. Of the 25 subjects with both a positive pre-dose crossmatch and post-dose data, 24 subjects (96%) converted to a negative crossmatch with treatment. The remaining subject had a borderline positive crossmatch but was nevertheless transplanted.

**Table 38 Summary of crossmatch conversion in transplanted patients by study**

| | Any positive crossmatch test, predose, n (%) | Any positive crossmatch test, postdose, n (%) |
|---|---|---|
| **Study 02 N=1** | 1 (100) | 0 (0) |
| **Study 03 N=10** | 6 (60) | 0 (0)[a] |
| **Study 04 N=17** | 14 (82) | Not determined |
| **Study 06 N=18** | 18 (100) | 1 (6) [b] |
| **All highly unlikely to be transplanted N=38** | 35 (92) | 1 (3)[b] |

[a] 3 subjects were not analysed for post-dose crossmatch

[b] Borderline flow crossmatch and negative virtual crossmatch – judged as not clinically significant

Elimination of anti-HLA antibodies

**Table 39** summarises the number and proportion of exposed patients (transplanted and not transplanted) with all positive SAB-HLA antibodies having median MFI value <2,000 at different timepoints. Data is available for 53/56 subjects. 1/53 (1.8%) had median MFI value <2,000 for positive SAB-HLA antibodies.

In the lowest dosing group in Study 02, 0.12 mg/kg (N=3), one subject (33%) shifted to median MFI value <2,000 whereas the other two subjects remained with median MFI ⩾2,000. Among the 50 subjects treated with 0.24-0.5 mg/kg, 47 (94%) shifted to median MFI <2,000.

**Table 39 Number and proportion of patients with all positive SAB-HLA antibodies having median MFI value <2,000**

| Time-point | **Study 02 0.12 mg/kg N=3** | **Study 02 0.25 mg/kg N=5[a]** | **Study 03 0.25 mg/kg N=5** | **Study 03 0.50 mg/kg N=5** | **Study 04 0.24 mg/kg N=17** | **Study 06 0.25 mg/kg N=18** |
|---|---|---|---|---|---|---|
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Pre-dose | 0 (0) | 1 (20) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| 1 h | 0 (0) | 4 (80) | 3 (60) | 5 (100) | 6 (35) | - |
| 2 h | 0 (0) | 4 (80) | 5 (100) | 5 (100) | - | 9 (50) |
| 6 h | 0 (0) | 4 (80) | 5 (100) | 5 (100) | 9 (53) | 15 (83) |
| 24 h | 1 (33) | 4 (80) | 5 (100) | 5 (100) | 15 (88) | 18 (100) |

[a]1 patient received only 1/3 of the dose

DSA elimination

Pre-dose DSA with MFI >2,000 was reported for 43/46 (93%) transplanted subjects. 38 of these 43 subjects (88%) had no DSA with an MFI value > 2,000 at 24 hours after administration (**Table 40**).

According to the applicant, the signal seen in MFI for the five remaining patients was due to the presence of scIgG. The crossmatch tests for these subjects were converted to negative and they were all successfully transplanted.

**Table 40 Number and proportion of transplanted patients with DSA and patients with all DSA MFI values <2,000**

| | **Study 03 0.25 mg/kg N=4** | **Study 03 0.50 mg/kg N=4** | **Study 04 0.24 mg/kg N=17** | **Study 06 0.25 mg/kg N=18** |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) |
| Pre-dose | 1 (25) | 0 (0) | 2 (12) | 0 (0) |
| 1 h | 4 (100) | 3 (75) | ND | 8 (44) |
| 2 h | 4 (100) | 3 (75 | 14 (82) | ND |
| 6 h | 4 (100) | 4 (100) | 15 (88) | 11 (61) |
| 24 h | 4 (100) | 4 (100) | 16 (94) | 14 (78) |

Patient and graft survival

All subjects were alive and 43/46 (93%) of the grafts were functioning at 6 months.

Three subjects lost their grafts; one subject in Study 04 and two subjects in Study 06.

- *Subject:*

The subject had a previous transplant that lasted for 18 years before being lost due to chronic rejection. The patient was highly sensitized with cPRA >95% (MFI >2,000 cut off) pre-dose, which changed to no MFI value >200 with very low IgG concentration and completely cleaved to F(ab')2 and Fc, 24 hours after imlifidase treatment. Immediately after surgery, as soon as the circulation restarted, the kidney turned black and swollen, and was removed. Pathology revealed evidence of hyperacute rejection, but no DSA or HLA antibodies were found in serum. A strong IgM antibody of unknown specificity binding to pathologically relevant targets in the kidney was detected. Since no IgG staining was detected after incubating the subject's serum with the donor kidney, it was concluded that the event was not related to the study drug.

- *Subject:*

At pre-dose, the patient had 2 class II DSAs, one at 2,500 and another at 4,300 MFI, and was FCXM positive for B cells. After dosing with imlifidase, the crossmatch became negative. The kidney never started to produce urine. Delayed graft function was reported with start on Day 3 and dialysis started on the same day and continued throughout the study.
On Day 9, a non-biopsy proven suspicious AMR was treated with methylprednisolone. On Day 10, a graft rejection episode occurred and one DSA (HLA-A31) rebounded around Day 14. About 2 months after transplantation, a nuclear medicine renal scan revealed a non-functioning transplanted kidney. The patient was admitted to hospital at Day 76, where signs of cell mediated rejection (CMR) were seen. A nephrectomy was performed 2 days later.
The patient, who had been transplanted once before, had been in dialysis for 9 years and had a medical history of Wegener's syndrome, anti-neutrophil cytoplasmic antibody-positive vasculitis, and severe hypotension. The hypotension caused problems during surgery with poor perfusion of the allograft and subsequent loss of the kidney; this primarily due to complex pre-existing medical conditions that precluded administration of rituximab to prevent DSA rebound and severe hypotension posttransplant.

- *Subject:*

At pre-dose, the patient had 1 class II DSA at 10,500 MFI and was flow crossmatch positive for B cells. After dosing, the crossmatch became negative.
Delayed graft function was reported with start on Day 2 and dialysis started the same day and continued throughout the study. The patient was treated with methylprednisolone and plasmapheresis (Day 28) and IVIg (Day 34) for rejection. On Day 120, the patient was hospitalized and the presence of chronic active AMR and active CMR (SAE) was established (biopsy proven). The treatment included IVIg. The kidney never started to produce urine after transplantation, and the graft was considered to be lost on Day 120.
The patient had been in dialysis for 23 years, had Alport's syndrome, and a previous history of 3 failed kidney transplantations due to severe AMR, and thrombotic microangiopathy. The second and third allografts never started to function. The present graft loss was complex due to numerous pre-existing medical conditions that contributed significantly to not having a successful transplant.

The baseline characteristics for these three subjects are summarised in **Table 41**.

**Table 41 Baseline characteristics of patients suffering graft loss**

| | **Study 04 Patient** | **Study 06 Patient** | **Study 06 Patient** |
|---|---|---|---|
| **Donor** | Deceased | Deceased | Deceased |
| **cPRA (MFI cut-off 2000) (%)** | 95.81 | 92.02 | 100 |
| **FCXM T-cell** | Negative | Negative | Negative |
| **FCXM B-cell** | Positive | Positive | Positive |
| **KDPI (%)** | 73 | 5 | 34 |

The kidney donor profile index (KDPI) combines a variety of donor factors, e.g. age, weight, morbidity, renal function, cause of death into a single number that summarizes the likelihood of graft failure after deceased donor kidney transplant. For example, the KDPI of 73% reported for one subject indicates a higher expected risk of graft failure than 73% of all kidney donors recovered the year before.

The hyperacute rejection in one subject was not IgG mediated and could thus not be considered lack-of efficacy for imlifidase.

The two subjects in study 06 were diagnosed with delayed graft function. Neither of the subjects could be taken out of dialysis during the study. Both subjects were treated for AMR starting day 9 and day 28 respectively. The rejection episodes may have contributed to the graft loss; however, in both cases, complicating factors are present.

The Applicant notes that it is not possible from the three patients with graft losses to conclude on subpopulation differences in graft survival.

Kidney function

Estimated glomerular filtration rate (eGFR) calculated from serum creatinine was used as an outcome measure for kidney function and was assessed for all transplanted patients (**Table 42**). 90% of the 42 subjects with a functioning kidney and eGFR data collected at the end of study had an eGFR ≥30 mL/min/1.73 m2, corresponding to 83% of all transplanted subjects.

**Table 42 Kidney function categorised by eGFR at 6 months**

| | eGFR category | | |
|---|---|---|---|
| | ≥60 mL/min/1.73 m2 | 30-59 mL/min/1.73 m2 | <30 mL/min/1.73 m2 |
| | n (%) | n (%) | n (%) |
| Study 03 N=10 | 2 (20) | 6 (60) | 2 (20) |
| Study 04 N=16 | 9 (56) | 6 (38) | 1 (6) |
| Study 06 N=16 | 4 (25) | 11 (69) | 1 (6) |
| All N=42 | 15 (36) | 23 (55) | 4 (9) |

The applicant provided subpopulation analyses to investigate any correlation between renal function at different timepoints and expected likeliness to be transplanted, gender, age or donor status. Renal function was stratified in three groups; <30, 30-59 and >60 mL/min/1.73 m2. Due to the limited number of transplanted subjects, the number of subjects in each subpopulation is very small. There

was a trend towards better renal function in female recipients and recipients with living donors, however, no conclusions can be drawn.

Antibody-mediated rejections

An acute rejection episode is the consequence of an immune response of the host attacking the transplanted organ or cells. The response can be of cellular (primarily T lymphocytes) (CMR) and/or humoral (circulating HLA- and non-HLA-antibodies) (AMR) origin.
An acute rejection is clinically suspected in patients with an increase in serum creatinine or increased proteinuria after the exclusion of other causes of graft dysfunction, and the diagnosis is generally confirmed by biopsy. The Sponsor adjudicated all reported potential AMRs and CMRs based on the Banff 2017 criteria. The adjudication was unblinded, consistent with the studies being uncontrolled.

15/46 (33%) subjects had at least one episode of antibody-mediated changes (**Table 43**) including the hyperacute IgM antibody-mediated rejection in one subject, discussed above.

**Table 43 Number and proportion of patients with AMR**

| | **Study 02 N=1** | **Study 03 N=10** | **Study 04 N=17** | **Study 06 N=18** |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) |
| Active/chronic AMR | 0 | 3 (30) | 2 (12) | 6 (33) |
| Subclinical AMR | 0 | 0 | 1 (6) | 2 (11) |
| Hyperacute rejection | 0 | 0 | 1 (6) | 0 |

The Applicant provided subpopulation analyses for AMR based on expected likeliness of being transplanted, pre-treatment crossmatch status, and baseline demographic characteristics were performed.

*AMR by transplantability*

Twelve successfully transplanted subjects experienced AMR. 10/12 (83%) subjects with AMRs were categorized as highly unlikely to be transplanted, which is the same proportion as the overall proportion of subjects (38 out of 46; 83%) in this category.
28 (74%) of the 38 transplanted subjects categorized as highly unlikely to be transplanted did not experience any AMR.

The number of identified DSAs in patients experiencing AMR varied from 1 to 11, and 3 (25%) of the subjects had 2 or 3 DSAs with MFI value > 2,000 at 24 hours post dosing.

*AMR by pre-treatment crossmatch status*

8 (73%) of the 11 subjects with active/chronic AMR were both FCXM T- and B-cell positive pre-dose, which is higher than the overall proportion of B+/T+ subjects among the transplanted subjects (14/46; 30%). None of the subjects with AMR were both B- and T-cell CXM negative.

*AMR by other subgroups*

**Table 44** summarizes the occurrence of AMR by demographics and baseline characteristics.

**Table 44 Summary of occurrence of active/chronic AMR by subgroup**

| Demographic characteristics | | All AMR N=11 n (%) | No AMR N=35 n (%) | Total N=46 n (%) |
|---|---|---|---|---|
| Age (years) | 18-<42 | 6 (55 | 16 (46) | 22 (48) |
| | 42-<65 | 4 (36) | 18 (51) | 22 (48) |
| | ≥65 | 1 (9) | 1 (3) | 2 (4) |
| Sex | Female | 5 (45) | 16 (46) | 21 (46) |
| | Male | 6 (55) | 19 (54) | 25 (54) |
| Region | EU | 6 (55) | 9 (26) | 15 (33) |
| | US | 5 (45) | 26 (74) | 31 (67) |
| Autoimmune disorders[1] | Yes | 3 (27) | 14 (40) | 17 (37) |
| | No | 8 (73) | 21 (60) | 29 (63) |

[1]HLGT='Autoimmune disorders' and PTs selected by medical review

There was a higher proportion of AMR in EU-patients compared to US patients, but no firm conclusions could be drawn due to the limited number of subjects in the subpopulation analyses.

No AMR was seen in subjects without positive crossmatch.

**Long term results**

***Study 14 – A prospective observational, long-term (5-year) follow-up study of patients treated with imlifidase prior to kidney transplantation in Studies 02, 03, 04 and 06***

A prospective observational, long-term (5-year) follow-up study (Study 14) of patients treated with imlifidase prior to kidney transplantation in Studies 02, 03, 04 and 06 is ongoing. The primary objective of Study 14 is to evaluate graft survival in patients and the secondary objectives are to evaluate long-term clinical outcomes including e.g. patient survival and kidney function. The number of acute rejection episodes, in accordance with the 2017 Banff classification, is a secondary endpoint.

Data are collected from entry in Study 14, i.e. from the end of the 'feeder' study. Any subject is assessed at each year-passage, i.e. patients with 3-year data are assessed also at 1 and 2 years.

Study 14 was still enrolling patients at the time for MAA, with preliminary data on 15 patients available at the time of initial submission. Additional results (cut-off date 30-Sep-2019) were provided during the procedure and are summarised hereafter.

At the cut-off date of 30-Sep-2019, 29 of the 46 patients transplanted in the feeder studies have been enrolled in Study 14.

Eleven subjects eligible for inclusion in the study (i.e. having received a renal transplant in studies 02, 03, 04 or 06) were not enrolled.

Six subjects denied study participation and five subjects could not be reached. For two of these subjects, limited information was available: one subject was known to be alive with a functioning graft 2 years after transplantation, and one subject in the complement population was known to be alive with a functioning graft 1 year after transplantation.

In addition, data were available for six subjects who lost their grafts or died before the start of Study 14.

The Applicant summarised data from Study 14 (1-year FU, 2-year FU, 3-year FU and 5-year FU), including two subjects not enrolled in the study but with additional data available and from the six subjects not included in the study due to death/graft loss. Data is lacking for several subjects at 1-year follow-up (FU), 2-year FU and 3-year FU, especially from the earlier studies 02, 03 and 04, since Study 14 was initiated after the end of the feeder studies. Moreover, not all subjects in study 06 has reached 2- and 3-year FU.

**Table 45 Disposition of follow-up visits (cut-off 30-Sep-2019)**

| | Study 02 N=1 | Study 03 N=10 | Study 04 N=11 | Study 06 N=13 | Total N=35 |
|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| Attended 1-year follow-up | 0 | 0 | 0 | 6 (46) | 6 (17) |
| Attended 2-year follow-up | 0 | 3 (30) | 1 (9) | 9 (69) | 13 (37) |
| Attended 3-year follow-up | 0 | 9 (90) | 6 (55) | 1 (8) | 16 (46) |
| Attended 5-year follow-up | 1 (100) | 0 | 0 | 0 | 1 (3) |

Three deaths were reported during this follow-up. These events were not considered related to imlifidase treatment by the Applicant.

Three events of graft loss were reported, all in the period 2-3 years after transplantation (all >31 months after transplantation). According to the Applicant, none of the events were related to imlifidase treatment, as two events occurred due to lowering or non-compliance with immunosuppressive medication, and the third was the eventual outcome of a prolonged delayed graft function. This information is acknowledged; however, the information available is considered too limited for secondary assessment.

In total, 17 of the 46 transplanted subjects in the studies were reported with a functioning graft at the 3-year FU, data was only available for 20 subjects in total.

1/19 subjects with eGFR data at 1-year FU had eGFR <30 ml/min/1.73 m2 compared to 1/16 at the 3-year FU. These numbers are not directly comparable due to the large number of missing values.

No antibody mediated rejection was reported after the 1-year FU.

Since it could be suspected that patients with a higher degree of sensitisation against their donor would have a higher risk for rejection episodes, which in turn may be a risk factor for worse renal function and shorter graft survival, the Applicant was asked to provide a subgroup analyses in highly sensitized patients who would not have been considered transplantable with their actual donor during the study based on DSA/positive crossmatch and that would be representative of the proposed target population.

The Applicant provided the requested subgroup analysis in patients "highly unlikely to be transplanted without imlifidase treatment" (HUT) based on the following 3 criteria:

- cPRA of ≥95% (as calculated using the Organ Procurement and Transplantation Network [OPTN] calculator) based on a mean fluorescence intensity (MFI) cut-off of 3000, or a historical peak PRA of ≥95%
- Deceased donor (DD) transplantation
- Positive XM (determined by CDC or flow cytometry XM test) towards the available graft immediately prior to imlifidase treatment and transplantation

The revised subgroup of patients defined as HUT comprises 25 patients (54%) with a median cPRA of 99.90%, including 2 patients in Study 03, 12 patients in Study 04, and 11 patients in Study 06.

Five of the 21 patients in the complement subgroup (non-HUT) fulfilled the cPRA and XM criteria but received a kidney from a living donor.

Analyses of incidence of graft survival, overall survival, kidney function and antibody-mediated rejection (AMR) within the revised subgroups are provided below.

Three graft losses occurred in the feeder studies (1 in the HUT population and 2 in the non-HUT population). Three graft losses were recorded more than 31 months after transplantation but before start of Study 14, 2 in the target (HUT) population and 1 in the complement (non-HUT) population (**Table 46**).

**Table 46 Death-censored graft survival by time period**

| | **0-6 months** | | **6 months–1 year** | | **1-2 years** | | **2–3 years** | | **3-5 years** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Graft survival** | **HUT N=25** n (%) | **Non- HUT N=21** n (%) | **HUT N=20[2]** n (%) | **Non- HUT N=18[3]** n (%) | **HUT N=16[2]** n (%) | **Non- HUT N=16** n (%) | **HUT N=8** n (%) | **Non-HUT N=12** n (%) | **HUT N=0** n (%) | **Non-HUT N=1** n (%) |
| **Yes[1]** | 24 (96) | 19 (90) | 20 (100) | 18 (100) | 16 (100) | 16 (100) | 6 (75) | 11 (92) | -- | 1 |
| **No** | 1 (4) | 2 (10) | 0 | 0 | 0 | 0 | 2 (25) | 1 (8) | -- | 0 |

HUT=highly unlikely to be transplanted, i.e. the target population

[1] Graft survival is assumed at earlier timepoints if 'Yes' at a later time-point.

[2] Including 2 subjects not enrolled in Study 14

[3] Including 1 subject not enrolled in Study 14

Three deaths have been reported, all in the target population, and all occurring in the period 7-12 months after transplantation. These deaths are included in **Table 47** despite occurring after the feeder studies and none of the patients being enrolled in Study 14. None of the deaths was regarded as having any relationship to kidney malfunction.

**Table 47 Overall survival by time period**

| | **0-6 months** | | **6 months–1 year** | | **1-2 years** | | **2–3 years** | | **3-5 years** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Survival** | **HUT N=25** n (%) | **Non-HUT N=21** n (%) | **HUT N=20[2]** n (%) | **Non-HUT N=18[3]** n (%) | **HUT N=15[2]** n (%) | **Non-HUT N=16** n (%) | **HUT N=8** n (%) | **Non-HUT N=12** n (%) | **HUT N=0** n (%) | **Non-HUT N=1** n (%) |
| **Yes[1]** | 25 (100) | 21 (100) | 17 (85) | 18 (100) | 15 (100) | 16 (100) | 8 (100) | 12 (100) | -- | 1 (100) |
| **No** | 0 | 0 | 3 (15) | 0 | 0 | 0 | 0 | 0 | -- | 0 |

HUT=highly unlikely to be transplanted, i.e. the target population

[1] Survival is assumed at earlier timepoints if 'Yes' at a later time-point.

[2] Including 2 subjects not enrolled in Study 14

[3] Including 1 subject not enrolled in Study 14

Kidney function assessments show that the majority of the patients have a satisfactory or well-functioning kidney (**Table 48**).

**Table 48 Kidney function by means of eGFR by year1**

| | **6 months** | | **Year 1** | | **Year 2** | | **Year 3** | | **Year 5** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **eGFR category (mL/min/ 1.73 $m^2$)** | **HUT N=17** n (%) | **Non- HUT N=15** n (%) | **HUT N=12** n (%) | **Non- HUT N=7** n (%) | **HUT N=12** n (%) | **Non- HUT N=8** n (%) | **HUT N=6** n (%) | **Non- HUT N=10** n (%) | **HUT N=0** n (%) | **Non- HUT N=1** n (%) |
| **<30** | 2 (12) | 2 (13) | 1 (8) | 0 | 1 (8) | 0 | 1 (17) | 0 | -- | 0 |
| **30-60** | 7 (41) | 10 (67) | 4 (33) | 6 (86) | 5 (42) | 7 (88) | 2 (33) | 6 (60) | -- | 1 |
| **60-90** | 8 (47) | 3 (20) | 7 (59) | 1 (14) | 6 (50) | 1 (12) | 3 (50) | 4 (40) | -- | 0 |

eGFR=estimated glomerular filtration rate, HUT=highly unlikely to be transplanted, i.e. the target population. The table includes transplanted patients with a functioning kidney, i.e. patients with graft loss or on dialysis are excluded.

[1] Some patients have data for later but not for earlier time points since the study was initiated after the end of the feeder studies. However, since data on kidney function could be retrieved from some of the patient's medical records, the total number of observations (N) at 1 and 2 years are greater than the number of actual visits. Only collected data are included in the table, no imputations are made.

The Applicant adjudicated all potential AMR reported based on the Banff 2017 criteria (Haas et al. 2018). At the adjudication, the following criteria had to be fulfilled to constitute an AMR:

- a biopsy was taken at the time of the AMR
- histological evidence of an AMR was reported in the pathology report
- presence of detectable levels of DSAs and/or evidence of antibody-mediated morphological changes in the kidney transplant at the time of the biopsy.

Adjudication of the rejection episodes reported in Study 14, showed that 1 of the proposed episodes, occurring in the period 6 months to 1 year after transplantation, fulfilled all the criteria to be classified as an AMR (**Table 49**).

**Table 49 Incidence of AMR by time period**

| | **0-6 months** | | **6 months–1 year** | | **1-2 years** | | **2–3 years** | | **3-5 years** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **AMR** | **HUT N=25** n (%) | **Non- HUT N=21** n (%) | **HUT N=18** n (%) | **Non- HUT N=16** n (%) | **HUT N=14** n (%) | **Non- HUT N=16** n (%) | **HUT N=8** n (%) | **Non- HUT N=12** n (%) | **HUT N=0** n (%) | **Non- HUT N=1** n (%) |
| **No** | 15 (60) | 16 (76) | 17 (94) | 16 (100) | 14 (100) | 16 (100) | 8 (100) | 12 (100) | -- | 1 |
| **Yes** | 10 (40) | 5 (24) | 1 (6) | 0 | 0 | 0 | 0 | 0 | -- | 0 |

AMR=antibody-mediated rejection, HUT=highly unlikely to be transplanted, i.e. the target population

***Study 13 - A retrospective study collecting data during 6 months follow-up from subjects who had participated in either Study 02 or Study 03 and received imlifidase prior to a kidney transplant.***

In this retrospective study, data were collected from subjects who participated in either Study 02 or Study 03, received imlifidase, and were transplanted. Historical data from donors and recipients, and data from the time of imlifidase administration and until 2 months (Study 02) or 6 months (Study 03) follow-up in the clinical studies were collected.

Efficacy endpoints were crossmatch test results at the time of imlifidase infusion, and kidney function, number of acute AMR episodes, and number and time of graft losses up to 6 months after transplantation.

The applicant indicated a discrepancy between the crossmatch test results presented in Study 03 and those presented in Study 13. The Applicant clarified that baseline crossmatch test status was incorrectly recorded for one single patient in Study 03 (T-cell FXCM was recorded as negative instead of positive, see Section 2.5.1, **Table 19**). This was discovered when preparing the data for follow-up Study 13. The Applicant confirmed that all other data has been checked and found correct. The error in recording is not considered to have any impact on the data. During the course of the study, inclusion criteria were changed to allow inclusion of more highly sensitised subjects. As the study was not randomised, the subjects were included in the dose group that was investigated at the time of their treatment. As a result, more subjects in the 0.5 mg/kg dose group had a positive crossmatch at baseline (4/5 in the high vs 2/5 in the low dose group).

***Numbers analysed***

All 10 subjects from Study 03 and the single subject transplanted after imlifidase treatment in study 02 were included.

***Outcomes and estimation***

Primary endpoint

There was no primary efficacy endpoint in Study 03.

Secondary outcome: Performance of Transplantation

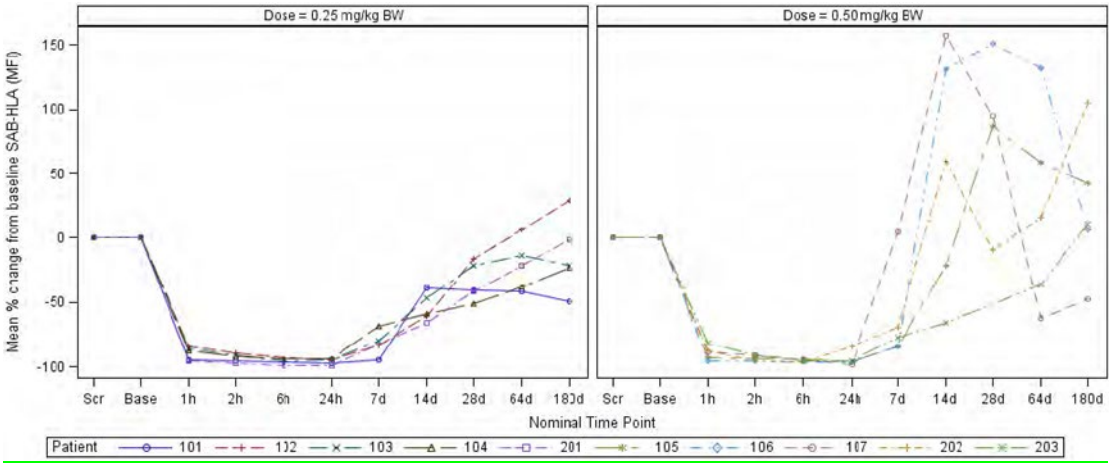
Patient eligibility for transplantation was assessed by the investigator based on HLA antibody levels and crossmatch tests after IdeS treatment and other factors, such as the expected cold ischaemic time and organ quality. Since no strict criteria for acceptable HLA antibody levels were defined, the performance of the transplantation was regarded as efficacy of imlifidase.

All 10/10 patients from Study 03 were found eligible for transplantation after IdeS treatment and all were transplanted; thus, both imlifidase doses (0.25 mg/kg and 0.50 mg/kg) resulted in HLA antibody levels acceptable for transplantation and negative crossmatch tests.

Secondary outcome: Anti-HLA Antibodies Analysed with SAB-HLA

Individual plots of the mean percentage change from baseline MFI of positive SAB-HLA antibodies are provided in **Table 50**.

**Table 50 Mean individual changes from baseline MFI of positive SAB-HLA antibodies – low dose group (left) and high dose group (right) (Study 03)**




The results from C1q-SAB analysis were congruent with the results from the LabScreen anti-HLA SAB analysis.

There was no DGF episode recorded in Study 02 or Study 03, and none of the subjects suffered a graft loss during the 6-months follow-up period. 4 (36%) of the 11 subjects experienced 7 suspected rejection episodes (reported as AEs/SAEs) within 4 months of transplantation. Biopsies were taken at 6 of the episodes and 3 (27%) subjects had biopsy-confirmed AMR with C4d depositions and presence of DSAs, while 2 were regarded as CMR and 1 as a mixed AMR/CMR.

Secondary outcome: Donor Specific Antibodies

All individual DSAs in all patients declined rapidly from pre-dose to 1 hour after dosing and remained low until 24 hours in all patients and day 7 in most patients. One subject had a more rapid recovery of DSA.

Data on DSA for all transplanted subjects are given under heading

*Analysis performed across trials (pooled analyses and meta-analysis)*.

Data on renal function and graft survival for all transplanted subjects are given under heading *Analysis performed across trials (pooled analyses and meta-analysis)*.

## Clinical studies in special populations

No clinical studies in special populations were performed. The mean age in Study 02, 03, 04 and 06 was 44 years, ranging from 20 to 73 years of age with only 3 subjects being older than 64 years of age. Two of the subjects >64 years old were transplanted.

## 2.5.3. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

The clinical development programme for imlifidase consists of four Phase II studies (**Study 02**, **Study 03**, **Study 04** and **Study 06**). All four studies are small and uncontrolled.

The applicant argues that a double-blind, randomized, controlled study to support the efficacy of imlifidase in the proposed highly sensitized target population is not feasible since it would require randomization of patients to a known non-satisfactory comparator desensitization strategy, i.e. a strategy that is highly unlikely to be successful, at least within the short time-frame available for transplantation of a deceased donor organ. Patients should not be subjected to a cumbersome and potentially harmful treatment and valuable organs should not be transplanted without high likelihood of success. This was agreed upon by CHMP. However, CHMP considers that comparisons to other groups of transplanted subjects are still of interest for the long-term benefit/risk assessment as further discussed below.

The applicant clarified that deceased donor kidneys were allocated against HLA mismatch and XM positivity because imlifidase was known to be available at the site. Otherwise, these patients would not have been offered a kidney and transplanted without imlifidase.

Aspects on dosing

The selection of imlifidase doses for Phase II investigations was based on data from 20 healthy men in a single phase I study (**Study 01**), a randomized, placebo-controlled (within each cohort) dose escalation study. This study was terminated (prematurely), testing the dose of 0.24 mg/kg as the highest dose, although the planned doses were set much higher, i.e. up to 1.2 mg/kg of imlifidase. The Applicant clarified that the dose was not further increased after it became clear that the 0.24 mg/kg dose already yielded the maximum effect.

In **Study 02**, different dosing regimens of imlifidase were investigated with the objective to find a regimen that decreases the anti-HLA IgG antibodies to a level that allows transplantation in the majority of patients. The dosing regimens were investigated for the ability and time frame to completely cleave IgG to its Fc and F(ab')2 fragments, in concentrations ranging from 2×0.12 mg/kg (24 hours apart), over 1×0.25 mg/kg to 2×0.25 mg/kg (24 hours apart). In a further Phase II single infusion **Study 03**, the dosing regimens comprised 2 single doses, 0.25 mg/kg and 0.50 mg/kg, in an attempt to find the appropriate dose that provides a sufficiently effective and rapid but still durable response. As in **Study 02**, the 0.25 mg/kg dose provided a rapid and effective response, leaving no intact IgG few hours after administration and the administration of 0.50 mg/kg in study 03 reached the same level of IgG elimination at a marginally shorter time, the lowest dose showing full activity in elimination of IgG was determined at 0.25 mg/kg.

Based on the results of **Study 02** and **Study 03**, a dosing regimen of a 15-minute IV infusion of 0.24/0.25 mg/kg imlifidase was chosen for the subsequent clinical **Study 04** and the main **Study 06**. Since 2×0.25 and 1×0.50 mg/kg had previously been investigated without any safety concerns, there was a possibility to add another dose of 0.24/0.25 mg/kg should the initial dose prove to be insufficient. Therefore, in 3 (of overall 19) patients of **Study 06**, a second dose of 0.25 mg/kg imlifidase (based on insufficient CXMs conversion after first 0.25 mg/kg dose) was administered. In one of these 3 patients administered 2x0.25 mg/kg BW, CXM conversion did not occur.

It is agreed by CHMP that the 0.25 mg/kg dose, given once is justified. Taking into consideration that imlifidase should be able to cleave also IgG-ADAs, and the PK properties of imlifidase, an effect of ADAs on the PD of imlifidase within the first 24 hours after first imlifidase is considered negligible. Therefore, upon CHMP request, the Applicant has included the possibility of a second dose in the SmPC in case the first dose does not provide the desired effect.

Aspects on design and methodology

The study design (uncontrolled, open-label) and methodology (e.g. descriptive statistics, partly retrospective analyses) of the **Studies 02, 03, 04 and 06** are acceptable considering the rarity and severity of the condition and the lack of a satisfactory comparator desensitization strategy. Renal

transplantation was part of the protocol for the latter three studies, as opposed to **Study 02**. Inclusion criteria for all studies included age ≥18 years, CKD stage 5 and that the subject should be active on the renal transplant waiting list; however, the eligibility criteria differed at several important points between the studies. In general, there were more exclusion criteria in **Study 03** than in the other two studies. However, this is not of concern since most of these exclusion criteria are generally considered contraindications for renal transplantation *per se*.

The overall primary efficacy endpoint for **Study 04** and the main **Study 06** was the ability of imlifidase to decrease the anti-HLA antibody level and convert a positive crossmatch (CXM) to negative within 24 hours to make the patient immediately eligible for kidney transplantation. Co-primary efficacy endpoints in **Study 04** and secondary efficacy endpoints in both studies aimed at graft survival and function (based on eGFR) up to 6 months after transplantation.
**Study 03** had no primary efficacy endpoint, but the secondary efficacy endpoints were congruent with the endpoints of **Study 04** and **Study 06**.

In the main multicentre **Study 06**, which was conducted in the USA, Sweden and France, 7 different CXM tests could be performed. Since the proposed indication requires that patients should have a positive crossmatch against an available deceased donor, the applicant was asked to clarify the relevance of the different CXM tests used in **Study 06** for transplantability, and the resulting benefit of conversion of these tests for the patients. For example, for Eurotransplant, only a positive CDC crossmatch represents a clear contraindication for organ allocation. The applicant clarified that the different XM tests are basically variants of 3 different techniques, cell-based flow cytometry (FCXM), cell-based complement-dependent cytotoxicity (CDCXM) and virtual crossmatch (vXM) based on single antigen bead analysis. Different methods for XM determination are currently in use at certified laboratories at different transplant centres, but the current clinical practice at most transplantation centres is FCXM using T- and B-cells from the donor. This method is considered more sensitive than CDCXM, which is also associated with a high risk of false positive results due to non-discrimination between IgG and IgM antibodies, dependence on reader, and lymphocyte viability (Kumar et al. 2017). Since vXM is a theoretical estimation of the crossmatch, this method only gives a preliminary result that should be confirmed by FCXM and/or CDCXM. There are different opinions of the (most) appropriate assays for XM testing (Tait et al. 2013). It is acknowledged that some regions, national authorities, and allocation systems specify which test is to be used. For example, Eurotransplant which covers 8 of the EU countries (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia) mandates the CDCXM, while in other countries the certified laboratory (clinical immunology and transfusion medicine at the hospital performing the organ transplantation) can decide which XM test to be used to make the decision to transplant. All certified laboratories have to follow the same guidelines on how to perform and interpret results from FCXM, CDCXM, and other techniques used in the clinical decision making. In all cases, the responsible transplant physician will ensure that the relevant data are generated to provide the basis for the decision to transplant or not. The Applicant was unable to recommend a specific crossmatch test, because different crossmatch tests (FCXM or CDCXM, both relevant) are being used at the certified laboratories at different transplant centres for determining crossmatch status. FACS-B was the most commonly employed XM test in study 06. However, different XM tests are in use for the purpose of kidney allocation and transplantation. After considering the responses of the Applicant, the CHMP agreed that the use of imlifidase should not be tied to the use of a specific XM test.

With regards to the patient benefit, the most important efficacy endpoints are considered (long-term) graft survival and graft function. Although, it is acknowledged that the effect of a single dose of imlifidase is timely limited and the long-terms prospect of a transplanted kidney largely depend on subsequent immunosuppressive therapy and other factors (e.g. quality of the donor kidney),

crossmatch conversion and transplantation *per se* is only beneficial if the transplanted organ survives and functions.

No formal sample size calculation was performed in any of the studies. The total sample size of this application is very sparse (N=56 imlifidase treated subjects). In order to address this, the applicant agreed to conduct a post marketing efficacy study (as discussed under "Additional efficacy data needed in the context of a conditional MA").

**Study 13** was a retrospective study aiming to provide background information on subjects transplanted within **Study 02** and **Study 03**.

Aspects on study conduct

No formal statistical testing was performed in any of the studies, the analyses are merely descriptive. This is in principle acceptable for the studied condition and a CMA application. However, there were some unclarities that had to be addressed by the Applicant:

- It is stated in the SAPs that missing data were not to be imputed, however it seems that at least missing eGFR data in **Studies 04** and **06** were imputed with LOCF. This was not considered acceptable by CHMP. In their response, the applicant provided the requested alternative analyses using observed cases only. These new analyses did not have an impact on the results regarding kidney function.
- According to the protocol in **Study 04**, a transplant biopsy should be performed at Day 180. However, for 9/16 subjects (one subject with graft loss excluded) "missing data" were recorded for Day 180 biopsy. Two subjects discontinued the study. The Applicant explained that 12 of the remaining 14 patients in **Study 04** had a biopsy taken, 7 of whom provided an evaluable end-of-study biopsy assessment for the purpose of the clinical study. The reasons for not receiving any biopsy data for these 7 patients were:
    - 3 patients did not consent to share the data
    - 2 patients were out of the acceptable time window at the last visit
    - 2 patients were not biopsied due to refusal of biopsy by one patient and hydronephrosis at the time of end-of-study in the other patient

Furthermore, it is noted that the original SAP in **Study 03** is claimed to have been finalised before data base lock. However, it was finalised after last subjects last visit when all data must be assumed to have been available in this open label study. This is also true for the **Study 06**.

**Efficacy data and additional analyses**

In the main **Study 06**, CXM conversion was observed in 17 of the 19 patients treated with imlifidase (0.25 mg/kg), administered once or twice. All 17 patients were subsequently transplanted (89.4%) and received a deceased or live donor organ. In addition, one subject with a borderline crossmatch after treatment was considered transplantable based on the totality of data. The one subject that was not transplanted received only 25% of the imlifidase dose due to an infusion reaction. It can be concluded that imlifidase was overall successful in achieving CXM conversion within 24 hours. However, the time to CXM conversion could not be calculated due to many missing values for the CXM test during the 24 hours after imlifidase infusion.

Efficacy results for all transplanted subjects (across studies)

Even though the four studies have differences in design, it is considered acceptable to pool data from transplanted subjects of these studies. All transplanted subjects received 0.25 or 0.5 mg/kg of imlifidase. Data on achieving transplantability in sensitised subjects and especially outcome after transplantation with regard to graft survival and graft function are considered the most clinically relevant parameters.

*Transplantability*

In total, 56 subjects were exposed to imlifidase in the studies. 45 of the 46 subjects (98%) planned for transplantation in the main studies were successfully transplanted.
The remaining subject in Study 06 received only approximately 25% of the planned imlifidase dose due to an infusion reaction and was therefore not transplantable. On the other hand, one subject from Study 02, where transplantation was not part of the protocol, was offered an organ and was transplanted after imlifidase treatment.

The applicant claimed initially that all subjects in **Study 04** and **Study 06** and three subjects from the earlier studies, i.e. 38 subjects, represent a population of patients "highly unlikely to receive any compatible kidney transplant" based on the cPRA, presence of DSA and crossmatch, and history of unsuccessful transplantations. It is understood by CHMP that such estimates are based on the totality of data; however, in **Study 06**, 3/19 subjects (16%) were reported to have cPRA <80%, i.e. not fulfilling the definition of being highly sensitised. Further, two of the subjects in **Study 04** had neither any DSA with MFI >2,000 nor a positive B-or-T-cell FCXM to their respective donors, in spite of high cPRA (87.8% and 99.6% respectively).
The eligibility criteria in the earlier studies did not specify a certain "breadth" of immunisation, resulting in the inclusion of subjects with known HLA antibodies precluding transplantation with the actual donor but with values for panel reactive antibodies (PRA) not indicating that the subjects were highly sensitised, i.e., it might not have been impossible to find a suitable donor.
39/46 (85%) transplanted subjects had a positive crossmatch before imlifidase treatment.

The Applicant was asked to provide further reassurance that the study population is representative for the target population and the effects of imlifidase are not overestimated. It is likely that patients with a high degree of sensitisation against their donor will have a higher risk for rejection episodes, which in turn is a risk factor for worse renal function and shorter graft survival. The applicant provided subgroup analyses in patients considered "highly unlikely to be transplanted without prior imlifidase treatment" (HUT) and in the complementary "non-HUT" group. The 3 criteria used to define HUT were cPRA ≥95% based on an MFI cut-off of 3000 or historical peak PRA > 95%, deceased donor, a positive XM (CDCXM or FCXM). This HUT patient population definition is agreed by CHMP to reflect more closely the target population. Results in this subgroup (N=25) were compared to the remaining patients (non-HUT, N=21).

As expected, the incidence of AMR was higher in the HUT subgroup: 7 (28%) vs. 4 (19%) patients had diagnosed AMR with clinical manifestations during the study. In addition, 3 patients (12%) in the HUT subgroup showed signs of AMR at the 6-month biopsy analysis but without any clinical signs, which was therefore categorized as subclinical AMR. Overall, the AMR frequency in the HUT group was approximately twice the frequency in the complement subgroup. However, the applicant highlights that the frequency of AMR in highly sensitised patients desensitised with imlifidase is similar to the frequencies reported in the literature for sensitised patients being desensitised and transplanted. The references provided to support this statement reported highly variable AMR incidences between 12% and 61%. Despite the higher frequency of AMR in the HUT subgroup, there was no difference in kidney function at 6 months between this group and the complement subgroup and graft loss was not increased, indicating that the episodes of AMR were successfully treated. However, data on longer-term outcome are still scarce.

*Graft survival*

Overall graft survival at six months was 93%; 3/46 subjects (6.5%) of the transplanted subjects experienced graft loss; two subjects in **Study 06** and one subject in **Study 04**.

The one subject in **Study 04** experienced an IgM mediated hyperacute AMR that cannot not be considered lack-of efficacy for imlifidase since imlifidase does not cleave IgM.
The two subjects in **Study 06** diagnosed with delayed graft function were not taken out of dialysis after transplantation. Both subjects were treated for AMR starting day 9 and day 28, respectively. In both cases, complicating factors were present, which are considered by the Applicant to be major contributors to the graft loss. It is agreed by CHMP that severe hypotension in one patient and a previous history of three failed kidney transplantations due to severe AMR and thrombotic microangiopathy in the second patient are more probable explanations for graft loss in these cases than a lack of efficacy of imlifidase. However, the AMR episodes may have contributed to the outcome.

In a publication by Shaffer et al (Transplantation Direct 2016), 29 sensitised subjects with pretransplant DSAs and a positive crossmatch, i.e. a population similar to that of the imlifidase development programme, were followed for a mean period of 1,048 ± 574 days after transplantation with living donors after desensitisation with IvIG and rituximab. In this population, 3-year graft survival was 95%.
In the very limited long-term data from ongoing **Study 14**, no additional graft loss has been reported during follow-up. These data are encouraging and sufficient to support a conditional marketing authorisation. However, additional data are required post-marketing to confirm the long-term positive effects.

The Applicant notes that it is not possible from the three patients with graft losses to conclude on subpopulation differences in graft survival. This is agreed by CHMP.

*Graft function*

42 out of 46 (91%) transplanted subjects had a functioning kidney and eGFR data collected at the end of study (6 months). Of these, 90% had an eGFR ≥30 mL/min/1.73 m2 (corresponding to 83% of all transplanted subjects).
For comparison, the Applicant provided data from Keong et al 2016, analysing results from 15,778 kidney transplant recipients between the years 2004 and 2006 in the American UNOS (United Network for Organ Sharing) database. The UNOS population collects data from the general transplant population in the US and is thus not a highly sensitised patient population. 43% of the subjects analysed had received a kidney from a living donor. 95% out of the 15,778 transplanted patients had an eGFR ≥ 30 mL/min/1.73 m2 at 6 months after transplantation. Taking into consideration that the study population treated with imlifidase exhibited a higher degree of sensitization and received a

higher proportion of deceased donor organs, the difference in renal function between the imlifidase treated subjects and the UNOS population is not considered remarkable. It should however be noted that the UNOS data is from subjects transplanted 2004-2006, and it is conceivable that the general graft survival has improved during the last decade.
This is agreed by CHMP since 5-year follow-up information will be collected post-marketing to allow for a conclusion on long term graft survival and kidney function.

The Applicant provided subpopulation analyses to investigate any correlation between renal function at different timepoints and expected likeliness to be transplanted, gender, age or donor status. Renal function was stratified into three groups; <30, 30-59 and >60 mL/min/1.73 m2. Due to the limited number of transplanted subjects, the number of subjects in each subpopulation is small. There was a trend towards better renal function in female recipients and recipients with living donors, however, no firm conclusions can be drawn.

*Antibody-mediated rejection (AMR)*

15 out of the 46 (33%) transplanted subjects had at least one episode of antibody-mediated changes including the hyperacute rejection in one subject (as discussed above).
11/46 subjects (24%) experienced biopsy-proven AMRs combined with clinical signs, defined as active and/or chronic AMRs, while 3 events (6.5%) were identified on analysis of a biopsy without any clinical signs and defined as subclinical, thus would not have been detected without protocol biopsies.
However, also subclinical AMR should be diagnosed and treated early to improve outcomes after kidney transplantation (Parajuli S, et al., Transplantation 2019). As discussed above, HUT patients had more frequent AMRs that were manageable.

The overall AMR frequency of transplanted kidneys in the scientific literature is difficult to establish, as the populations in different publications differ by grade of sensitisation, proportion of deceased donors and observation time. The time period during which the transplantations were performed is also of interest as the efficacy of the immunosuppressive therapy has constantly improved. Inclusion of chronic AMR may also differ.
According to the applicant, AMR frequencies of 25-60% are reported in the literature. Lower frequencies are reported in other publications, e.g. by the Organ Procurement and Transplantation Network (OPTN) reporting that the incidence of acute rejection among first-year posttransplant patients decreased from 10 percent in 2009 to 2010 to 8 percent in 2013 to 2014 (OPTN/SRTR 2015 Annual Data Report: Kidney; Hart et al, 2017).
Of special interest is the article by Shaffer et al discussed above, with a study population similar to the imlifidase study population. In this publication, 4/29 subjects (14%) transplanted from November 2009 to September 2014 experienced an acute rejection during the three-year follow-up period, of which 2 (6.9%) were classified as AMR.

All patients experiencing AMR in the studies were successfully treated according to local practice. Notwithstanding, episodes of AMR are of importance for graft survival. According to Lefaucheur et al (J Am Soc Nephrol. 2010), the 5- and 8-year graft survivals of patients who had an episode of AMR were 54.3 and 45.5%, respectively, and therefore significantly worse than that of the remaining transplant population (88.5 and 81.9%, respectively; P <0.0001). The Applicant agrees to evaluate long-term fate of transplanted kidneys in a 5-year post-marketing study in imlifidase-treated patients.

In subpopulation analyses, there was a higher proportion of AMR in EU-patients compared to US patients (40% vs 16%), but no firm conclusions could be drawn due to the limited number of subjects. No AMR was seen in subjects without positive crossmatch, indicating a greater risk for AMR with positive crossmatch which is plausible. This is in line with the findings of Gloor et al (Am J Transplant 2010) comparing 119 positive crossmatch (+XM) compared to 70 negative crossmatch (−XM) living

donor kidney recipients transplanted between April 2000 and July 2007. AMR occurred in 49/119 +XM patients (41%) a median of 7.5 days post-transplant, compared to one −XM patient (p = 0.0001).

**Bridging between clinical study material and product to be marketed**

The clinical studies were performed with imlifidase manufactured by process 1, whereas material from Process 2, the intended commercial product, has not been used in any of the clinical studies. Since material from the two processes differ in pharmacological activity, formulation and impurity profile (reference is made to the quality part of this report), the relevance of clinical data generated with process 1 material to the product to be marketed was questioned. For bridging purposes, the Applicant provided a comprehensive quality comparison, non-clinical in vitro studies as well as a new PK/PD study in healthy subjects using process 2 material. A head-to-head comparison was not possible because process 1 material was no longer available. Based on these data it can be concluded that process 2 material is purer with an approximately 2-fold potency compared to process 1 material. However, in non-clinical *in vitro* studies under physiological conditions, i.e. using patient sera, no differences in IgG degradation could be observed, which was attributed to the presence of pre-existing ADAs. The PK profiles did not suggest equivalence but, more importantly, PD responses were largely similar. Based on the observation that the effects of process 1 and process 2 material appear to be similar under physiological conditions and that imlifidase is highly specific for cleaving IgG without known or suspected off-target effects, the clinical performance of the clinical and the to be marketed version is expected to be comparable.

A number of details in the study design and/or methodology of one or more of the studies of the clinical development programme that may have impact on the use of imlifidase in clinical practice, were initially not reflected in the proposed SmPC. The Applicant agreed to adapt the SmPC in line with study requirements, specifically:

- Exclusion criteria applied in all three studies regarding different active infections, including but not restricted to, positive HIV-test, active HBV, are reflected as warnings in the SmPC.
- In **Study 04**, but not in **Studies 03** and **06**, inclusion criteria comprised pre-transplant vaccination with *Streptococcus pneumoniae* and *Neisseria meningitides*. Likewise, recent vaccination with live attenuated vaccine(s) was an exclusion criterion in **Study 04** but not in the other two studies. The Applicant clarified that these eligibility criteria reflected the standard routines in kidney transplantation at the site rather than being selected based on the intervention with imlifidase. It is therefore agreed by CHMP that there is no need to amend the SmPC with the corresponding information.
  The Applicant was also requested to discuss whether imlifidase, in combination with other immunosuppressive agents may be associated with a risk of reactivation of latent tuberculosis The Applicant considered that there are no indications that imlifidase treatment would increase the risk for reactivation of live attenuated vaccines. The Applicant agrees that all depleting agents and immunosuppressive drugs carry an increased risk of infection to the imlifidase treated subjects. It is however pointed out that no case of infection with tuberculosis or any reactivation of live-attenuated vaccines have been observed so far in the clinical development programme of Idefirix. Furthermore, the Applicant pointed out that the proposed immunosuppressive treatments leave the innate immunity system largely intact and that treatment with rituximab does not affect plasma cells as these do not express CD20. In support of this, is **Study 01** a phase I study in healthy volunteers confirming a steady return of vaccine antibody titre levels starting around 2 to 3 days after treatment reaching normal levels around 2 months. The Applicant included the potential risks of extensive immunosuppressive treatment in the SmPC Section 4.4 to alert on the potential risk of reactivation of live-attenuated vaccines and/or latent tuberculosis. This is agreed by CHMP.

- In both **Studies 04** and **06**, subjects were given intravenous immunoglobulin (IVIg) 7-21 days after imlifidase. Additionally, in **Study 06**, a single dose of rituximab was administered at Day 9 for the purpose to prevent or blunt the rebound of donor specific antibodies. These additional treatments are included in section 5.1 of the SmPC with a cross reference from section 4.2 to 5.1.
- Prophylactic antibiotics were given in all studies to prevent opportunistic infections due to low IgG levels. The Applicant clarified that respiratory infections are the most common infections in patients with hypogammaglobulinemia and this is supported by the available study data. Therefore, a recommendation was added in the SmPC for the use of prophylactic oral antibiotics covering respiratory tract pathogens that should be added to the standard of care. A duration of 2 weeks was initially proposed. The Applicant extended the recommended duration of respiratory infection prophylaxis to 4 weeks since the median length of prophylaxis was 30 days (mean: 53 days; min-max: 0-180 days) in the clinical development for Idefirix. However, the mean and median treatment time given in the response do not only reflect prophylaxis given against respiratory infections. IgG-levels measured in **Study 15** (healthy volunteers) returned to approximately 50% of baseline 14 days after imlifidase treatment (mean 4.8 g/L versus 9.0 g/L at baseline. After 28 days mean IgG-levels were 6.7 g/L. The reference range for IgG differs somewhat between labs, but is normally around 6.5-16 g/L. These data support the use of prophylaxis for 30 days. The recommendation states also that antibiotic prophylaxis should be given for 4 weeks even though the patient was not transplanted. This is agreed by CHMP.
- According to the proposed text in section 4.2 of the SmPC, imlifidase should be administered "preferably within 24 hours prior to transplantation". Based on the results from **Study 02**, as well as **Study 03**, **Study 04** and **Study 06**, the Applicant was asked to present a recommendation for a clinically relevant timing of post-dose crossmatch test to avoid unnecessary delay of transplantation due to either too early or too late testing. The Applicant clarified that CXM tests can have variable turn-around times and this needs to be taken into account. The percentages of CXM conversion over time are presented in section 5.1 of the SmPC to provide an orientation for transplant centers. This is agreed by CHMP.
- The Applicant provided specific guidance at what time after imlifidase treatment the crossmatch can be expected to become negative, that at 2 hours after administration of 0.25 mg/kg imlifidase in 96% of the patients and after 6 hours at least 99.5% of the patients. A text regarding the time to XM conversion has been added in Section 5.1 of the SmPC. However, due to different methods used and variations in time to obtaining results at different transplantation centres, the decision when to run the XM test must be at the discretion of the transplantation team. A second dose can be administered immediately should it be decided to be needed.

### *Additional expert consultation*

The CHMP consulted experts in transplantation medicine to provide input regarding the definition of the target population that is most likely to derive benefit from treatment with imlifidase and the study population, design and endpoints of the PAES (obligation for a CMA).

Upon request from the CHMP, an ad hoc expert group meeting was convened on 21 April 2020.

**1) The proposed indication for Idefirix is '*desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased***

***donor'*. With respect to the proposed aim of treatment and target population, please discuss the following;**

**a) Please define the cut-off level(s) (for cPRA and/or other parameters) for the definition of high sensitization that are applicable for paneuropean practice in kidney transplant centers to trigger any of the desensitization management methods.**

The experts agreed that the criteria to trigger desensitization management methods depend on local settings, the main criteria to define cut-off being related to the size of the organ donor pool and thus the chance of receiving a HLA compatible transplant.

As an illustration, in Eurotransplant countries benefiting from a large pool of organs, desensitization would be justified for patients with cPRA>99.9% (cut-off would need to be discussed within the ETKAC group of Eurotransplant), while in smaller European countries such as Lithuania (2 transplant centers) patients with cPRA >80% would have a chance of transplantation that is low enough to justify desensitization.

Waiting time on the transplantation list (eg. Spain 1-year waiting period) and donor frequency are also parameters considered in some countries.

**b) Which of the systems and desensitization methods currently in place in the EU are reasonable to use in order to increase the chances of highly sensitized patients on the renal transplant list to receive a deceased donor organ and to be successfully transplanted? How frequently are they used and what are the success rates?**

The expert group agreed that for the setting of deceased donor transplantation there is no standard of care for desensitization methods of highly sensitized patients in current practice in Europe. Mismatch programs exist in some regions/countries (eg. Eurotransplant, Spain) that allow transplantation of highly immunized patients. The expert group stated that the acceptable mismatch programmes in Eurotransplant (ET) and PATHI (Programa for Access to Transplantation for Highly sensitized) have been shown to be a successful tool to enhance transplantation of highly sensitized patients. The experts acknowledged that there is a group of patients (ET has estimated 30%, Spain higher) that cannot be served in the current existing programs and that there is a need for additional options

**c) How frequent are (hyper)acute transplant rejection, delayed graft function and chronic antibody-mediated rejection (AMR) in highly sensitized patients having received a kidney transplant through the acceptable mismatch programme in the EU? What are the short- and long-term outcomes with regard to graft survival and graft function?**

The expert group stated that the (hyper)acute transplant rejection in highly sensitized patients having received a kidney transplant through the acceptable mismatch programmes in the EU should be extremely rare.

The expert group indicated that there are publications available reporting on the AMR rate in highly sensitized patients having received organs from a kidney transplant through the acceptable mismatch program.

With regards to graft survival, reference was to the publication from Heidt S. et al. 2018[1] which compared ten-year graft survival of patients with various sensitization grades who received a renal transplant through regular allocation to that of highly sensitized patients transplanted through the AM program. Graft survival in highly sensitized patients from the AM program was similar to those of the general kidney transplant population.

[1] Heidt, Sebastiaan, et al. "Kidney allocation based on proven acceptable antigens results in superior graft survival in highly sensitized patients." *Kidney international* 93.2 (2018): 491-500.

Overall, the expert group considered that the long-term outcome of kidney transplantation in highly sensitized patients in an acceptable mismatch program is excellent but limited to a part of highly sensitized cases. However, the concept of an acceptable mismatch program is not always possible and there are still patients (~30%) who cannot access to these programs or will not find an HLA compatible donor within these programs.

**d) Do you agree with the proposed target population for treatment with Idefirix? If not, how could the target population that could benefit from receiving imlifidase best be defined?**

The following input was provided by the expert group on the proposed target population:

- the group considered that the available data are not sufficient to support the use of imlifidase in the treatment of patients with positive T-cell CDC crossmatch testing, since only 2 patients with a documented positive CDC crossmatch have been transplanted following treatment with imlifidase. The experts highlighted that patients with positive T-cell CDC crossmatch have less successful graft transplantation outcomes, in particular higher graft loss than other transplanted patients. The experts noted that this patient subgroup is at the highest need for transplantation to be possible.

- the group noted that a part of the target population as defined in the currently available studies with imlifidase would not be automatically excluded from transplantation in current practice. The definition of DSA that preclude transplantation without desensitization varies largely between transplant centers. In the absence of other options many centers would accept patients with positive low to medium strength DSA in the LSA assay and allow transplantation without prior desensitization despite the possibly increased risk of acute or particularly chronic AMR. The Cedars Sinai group has also published successful transplantation of a crossmatch positive patient cohort very similar to the imlifidase treated group without additional desensitization next to IVIG and rituximab (Reinsmoen et al., 2008[2]).

- the group commented on the crossmatching testing and highlighted that flow cytometry is currently not the standard of crossmatch testing for Eurotransplant centers, but it is expanding in many countries (Spain); CDC crossmatch and in the near future single antigen bead assay are preferred methods.

The population defined by chance of transplantation will depend on the local definition of high risk which may be different across the EU regions.

**2) The Applicant is applying for a conditional marketing authorization and has proposed a postmarketing study to confirm the efficacy and safety of imlifidase in the proposed target population. The experts are asked to provide their views on the following aspects of such a study**

**a) Degree of sensitization (with regard to cPRA and/or other parameters) that should be required for the study population**

No inclusion criteria were proposed since the experts agreed that the benefit of highly sensitized patients to be transplanted and the risk associated is considered at the patient and at the local setting level. The inclusion should allow participation of patients with the lowest chances to be transplanted while, without jeopardizing the chances for patients to participate to mismatch program and might be combined. Recommendation was therefore given to apply for local inclusion criteria.

**b) Is a randomized study or a study with a concurrent control group considered feasible and appropriate? How could a concurrent control group be defined that would allow a meaningful comparison with the treatment group?**

[2] Reinsmoen, Nancy L., et al. "Acceptable donor-specific antibody levels allowing for successful deceased and living donor kidney transplantation after desensitization therapy." *Transplantation* 86.6 (2008): 820-825.

The experts consider that a randomized study to study imilifidase in highly sensitized patients with positive crossmatch is possible.

One suggestion was a study containing three arms. There was no consensus if this is feasible as no standard of care for desensitization in deceased donor kidney transplantation has been established. This study design would be to focus on a population with a negative CDC crossmatch, but with strong signs of immunization against donor antigens. This can be a positive flowcytometry crossmatch or a high level of DSAs (eg. total score when DSAs are present against multiple antigens or HLA class I A or B antigens). In this population, the risk of (early) antibody mediated rejection is increased and usually, immunosuppressive therapy is more intense (eg. by including induction therapy with anti-T and anti-B cell agents, although not universally applied in all patients). Also, the degree of sensitization would have to be low enough to allow rendering the crossmatch negative with a single session of plasmapheresis or immune absorption.

Three concurrent groups of highly sensitized patients are considered:

1. Current therapy according to local protocol (this should not include plasmapheresis / immunoadsorption)
2. Current therapy + imlifidase
3. A potential third arm would be: current therapy including plasmapheresis /immunoadsorption

The study population could include living donors as well as deceased donor kidney transplantations. It is suggested that the most appropriate endpoint would be the incidence (and timing) of antibody-mediated rejection, but also survival if the AMR could be solved. Sample size calculation should be performed; however, it is roughly estimated that 100-200 patients in both arms would be needed.

An alternative study within the Eurotranplant AM program was suggested. In the Eurotransplant region, patients can participate in the AM program once they have a dialysis time of more than 2 years **and** have a cPRA of > 85% (for the future ET is planning to change this rule for admittance to the AM program to chance of suitable donor from the donor pool of less than 2%). The experience indicates that 60-70% will find a suitable kidney with a negative CDC crossmatch within 2 years.

Patient waiting at least two years within the AM program would be randomized to the following arms:

1. Removal of unacceptable HLA types defined by antibodies detected in the LSA assay but that do not give a positive signal in the CDC crossmatch. This would lead to a higher chance of an organ offer. Transplantation would then be performed with imlifidase desensitization.
2. Continuation of waiting on the AM list for regular transplantation without changes to the unacceptable antigens within the AM program. Transplantation would then be performed without desensitization when a kidney with a negative crossmatch is found.

A higher transplantation rate with shorter waiting time would be expected in the imlifidase arm though complications after transplantation would possibly be higher. In view of the low chance of transplantation for the control arm, a benefit for the use of imlifidase could possibly be demonstrated despite the rejection risk possibly being higher. One option would be to focus on quality of life as primary endpoint, with patient survival as safety endpoint.

A similar strategy could be employed with a control arm composed of patients transplanted within the PATHI program which is based on avoiding unacceptable mismatch, and therefore has higher AMR than the AM ET program. It may therefore be more realistic.

References to publications related to the outcome of dialysis in Europe are provided in Annex. These should be considered when assessing the benefit of high-risk transplantations in comparison to remaining on dialysis treatment.

**c) The Applicant also proposes comparison with a historical control group recruited from the Collaborative Transplant Study (CTS) registry (2010 and up). Has medical care and clinical outcome of such patients relevantly changed since 2010 and which donor and recipient baseline factors/information would be most informative and thus important to be available to allow a meaningful comparison?**

The experts did not agree with the historical control group. Control patients from study centers would be preferred.

The experts agreed that immunosuppressive treatment has not changed for the last 10 years. However, practice has changed in the last 10 years and the understanding of the role of HLA immunization and the availability of single antigen bead assays has greatly increased in this period.

It is considered that limited information would be available from the historical control group. The experts pointed out that it is expected that the outcome of the DSA positive transplantation is worse than HLA compatible transplantation. This limits the lessons to be learned from the comparison with a control arm. Prior to the study, one would have to define which degree of poorer graft and patient survival in the desensitized patients would be acceptable.

One expert further stressed out that the CTS registry was not considered as the most suitable registry.

**d) The proposed primary study endpoint is 1-year graft survival, the key secondary endpoint is graft function. Based on the very limited data available, the Applicant assumes to reach a 1-year graft survival rate of approximately 80%. The experts are kindly asked for their view on the most appropriate primary and key secondary study endpoints considering both mechanism of action of imlifidase and patient benefit. Is the proposed 80% 1-year graft survival considered a realistic assumption? Would a lower graft survival rate still be considered beneficial?**

The group of experts considered that a 1-year graft survival rate of 80% would be below what is achieved in regular programs. However, considering the perceived risk of including highly sensitized patients, 1-year graft survival rate of 80% could be considered acceptable by the majority of experts in the proposed population. This was also supported by one patient representative (1 out of 3 patients expressed a view on the question). One expert noted that 80% was achieved several years ago by desensitization with other strategies and considers that imlifidase should offer better results. Glomerular filtration rate should also be needed to estimate longer survival.

The experts recommended to include protocol biopsy (at 3- and 12-months post-transplant) to assess development of chronic AMR.

In addition, the experts strongly recommended iBox as a secondary outcome evaluation.

**Target population**

The initially proposed indication was for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. However, the *ad hoc* expert group consulted during the procedure highlighted that in Europe (according to the most recent USRDS Annual Report 2017 including patients that started dialysis between 2007 and 2011), adjusted mean patient survival was 84.9% after one year, 74.4% after 2 years and 45.7% after 5 years of dialysis), and the risk of (early) antibody mediated rejection and graft loss is expected to be increased in highly sensitized patients not receiving a HLA-compatible graft. Therefore, it was not clear that earlier transplantation using imlifidase would be a benefit compared to staying on dialysis and waiting

for a matching graft. The Applicant clarified that imlifidase should be used as a complement to the existing allocation programmes for subjects anticipated to have a very low chance of finding a matching kidney despite the efforts within such programmes. The therapeutic indication in section 4.1 of the SmPC was revised to add the following restriction: *"The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritization programmes for highly sensitized patients".* As there are no harmonised approaches for deceased-donor organ allocation across the EU and the criteria for inclusion in an allocation system vary between the systems, the open wording in the amendment is agreed by CHMP, allowing for an individual assessment on the subject's possibilities of receiving a suitable graft within a reasonable time frame based on the local conditions irrespective of country or region in the EU. The Applicant argues that the HUT-population of the clinical development programme is representative for the target population. This is agreed by CHMP, based on the immunological characterization and a positive XM against an available deceased donor. Furthermore, for one of the studies, Study 04, the study population consisted of subjects who had previously failed to receive a transplant within Cedars Sinai's desensitization programme, supporting that study population was representative of a subset of highly sensitised subjects on the waiting-list.

The *ad-hoc* expert group (AHEG) consulted during the procedure cautioned about transplantation in T-cell CDCXM test positive ESDR patients (with or without imlifidase), since the outcome of HLA-incompatible transplantations has so far been poor. Patients with positive T-cell CDCXM tests are those with the highest level of sensitisation and the highest risk of (hyper)acute AMR and graft loss. The Applicant was asked to justify a positive benefit-risk balance also for subjects with a positive T-cells CDC crossmatch, as only three such subjects with a positive T-cell CDCXM test pre-treatment were included in the clinical development programme. The applicant clarified that this limited number of subjects was due to the CDC crossmatch not being used at all study sites. All three subjects with a pre-treatment positive T-cell CDC were transplanted after imlifidase treatment. One of these patients (06-402) received 2 doses of imlifidase before transplantation, but experienced no DGF, no graft loss, but an active AMR on day 10 to day 97 and a (subclinical) chronic active AMR on day 174 to day 377. The eGFR value was 92 mL/min/1.73m2 on day 174 and 72 mL/min/1.73m2 on day 669. The second patient (06-302) also received 2 doses of imlifidase but the CDCXM test was not repeated thereafter (only the FCXM test). Patient 06-302 experienced DGF on day 3 to day 28, no graft loss, but active AMR on day 7 to day 96, an active AMR and Borderline CMR on day 18 to day 96. The eGFR value was 37 mL/min/1.73m2 on day 174 and 47 mL/min/1.73m2 on day 771. The longer-term outcome of these patients is unclear. The third patient (02-102) experienced no rejection and no graft loss. eGFR value was 58 mL/min/1.73m2 on day 1828. In summary, only 3 patients had a positive T-cell CDCXM tests against the actual donor reported before imlifidase administration and one did not have a post-treatment CDCXM test. It can be concluded by CHMP that there is very limited experience in patients with a confirmed positive T-cell CDCXM before imlifidase treatment. The Applicant provided information on patient/graft survival, graft function and dialysis (in)dependence in these patients. All three subjects with a pre-treatment positive T-cell CDC were transplanted after imlifidase treatment. There are no indications from the very limited available data that the patient and graft survival for these three subjects were different from the overall study population. In this context it should also be remembered that there is rather a quantitative than a qualitative difference in the immune response between subjects with a positive T-cell CDCXM and subjects with any positive crossmatch but negative T-cell CDCXM. Therefore, there is no mechanistic rationale for a different effect of imlifidase on subjects with positive T-cell CDCXM. However, risk of (chronic) AMR is higher and long-term prognosis of HLA-incompatible kidney transplants may be poorer. The Applicant proposed to reflect in Section 4.4 of the SmPC that there is very limited experience in patients with a confirmed positive T-cell CDC-crossmatch test before imlifidase treatment. This is endorsed by CHMP. Additional data on positive T-cell based CDCXM patients against the donor should be gathered whenever possible in the planned 1-

year post-authorisation efficacy study (see "Additional efficacy data needed in the context of a conditional MA").

The available data support a conditional marketing authorisation, however, the long-term graft survival and graft function in patients transplanted with the help of imlifidase needs to be further addressed post-marketing.

### *Assessment of paediatric data on clinical efficacy*

No paediatric data submitted. The agreed PIP provides a deferral for submitting paediatric data.

### *Additional efficacy data needed in the context of a conditional MA*

The applicant commits to conduct and submit the final study report of Study 14 and a PAES as specific obligations to the CMA to provide comprehensive data.

**Planned post authorisation efficacy study (PAES)**

The Applicant provided a study synopsis for a non-randomised PAES in 50 imlifidase-treated patients and suggest comparison to a historical and a concurrent non-imflifidase treated control group treated at the same study sites and with different degrees of sensitisation.

Based on publicly available information, the CHMP noted that the Applicant has agreed with FDA to performing a randomized controlled trial (RCT) in patients with cPRA > 99.9%. The Applicant clarified that the aim of the study discussed with the FDA is to compare transplantation after imlifidase treatment with waiting for a suitable donor. Due to the effectiveness of the US KAS system, no methods for sensitisation are commonly used and standard of care is staying on the waiting list.

Further input on the proposed study and endpoints was given by the AHEG. As opposed to the Applicant, the experts considered an RCT in highly sensitized patients with positive FCXM but negative CDCXM test to be possible. The suggestion was to randomize such patients to transplantation using imlifidase versus staying on the (mismatch programme) waiting list until a suitable donor becomes available or being transplanted after desensitisation via plasmapheresis /immunoadsorption (done by only few transplant centers). The experts could not identify an ethical issue with such a RCT (primary endpoint at one year) since outcomes of patients on dialysis are considered generally good in in Europe (according to the most recent USRDS Annual Report 2017, including patients that started dialysis between 2007 and 2011, adjusted mean patient survival was 84.9% after one year, 74.4% after 2 years and 45.7% after 5 years of dialysis), and the risk of (early) antibody mediated rejection and graft loss is expected to be increased in highly sensitized patients not receiving an HLA-compatible graft. The expert group considered that the long-term outcome of kidney transplantation in highly sensitized patients in an acceptable mismatch program is excellent.

The Applicant explored the possibilities to perform a RCT with subjects active on the transplant waiting list randomized to transplantation with imlifidase versus continuing to receive standard of care until a suitable donor is found, similar to the US study planned together with FDA, or versus receiving a transplant using other desensitization methods. The Applicant emphasised the differences between the nationwide US kidney allocation system (KAS) and the situation in the EU without a common kidney allocation system. In an RCT, US subjects active on the KAS waiting list randomised to the control arm, i.e. remaining on SOC and waiting for a suitable organ offer, would have a substantially higher chance of receiving a matching kidney than the corresponding subjects in the EU. The Applicant argued that designing a RCT across European countries, in which highly sensitized ESRD patients are randomized to either imlifidase or (i) different, local acceptable mismatch (AM) programmes or (ii) to remain on the transplant waiting-list in countries where no AM programmes exists, would give rise to

considerable heterogeneity in the control arm making a meaningful comparison of the outcome data between the imlifidase-treated and control groups uninterpretable. Restriction of an RCT to a single or limited number of local AM programmes in an attempt to reduce this heterogeneity would result in data that would not be generalizable to other EU countries and regions where different allocation systems and AM programmes were used. The applicant further stated that no desensitisation protocols are currently approved as safe and effective within the EU in a deceased-donor setting and, thus, randomization to either imlifidase versus a chosen set of local desensitization protocols would result in a comparison of two unproven experimental treatments from which no clear conclusions could be reached. The Applicant concluded that, given the challenges of designing an RCT in Europe, a single-arm PAES documenting long-term outcomes of deceased-donor kidney transplantation between patients treated with imlifidase therapy and a matched, concurrent cohort of reference patients from the same investigational sites is preferred. This is agreed by CHMP.

The eligible patient population to the planned PAES includes subjects highly unlikely to be transplanted without imlifidase as defined by three criteria (highly sensitized patient with the highest unmet need based on the local allocation system and/or corresponding to a PRA of $\geq$ 95%, known DSA against an available deceased donor, positive crossmatch test (determined by CDC and/or flow cytometry) against an available deceased donor). The applicant explained the different cut-offs for defining a highly sensitized patient in different European countries and justified the rephrasing of the inclusion criterion. The inclusion criteria for the imlifidase-treated group are intended to reflect the clinical environment in which imlifidase will play a significant role, i.e. the transplantation setting with deceased-donor kidneys in the highly sensitized patients with no other option than an HLA-incompatible XM-positive transplant. The inclusion criteria are endorsed by CHMP.

A feasibility assessment performed by the applicant suggests that it would be difficult to recruit 100 patients from the narrowed population to the PAES study within a reasonable timeframe. Since the planned study is a specific obligation to the CMA to provide comprehensive data of a full marketing authorisation, it is considered important by CHMP that the study duration is not unnecessarily prolonged. However, the decrease in sample size results in a broad confidence interval. The applicant has therefore provided calculated confidence intervals for different sample sizes between 50 and 100 subjects, showing a relatively small narrowing of the calculated CI with an increase of sample size from 50 subjects (calculated two-sided 95%CI 0.663, 0.900) to 100 subjects (0.708, 0.873). A 50% increase in sample size from 50 to 75 patients gives a 95% CI of 0.692 to 0.884 representing, in absolute terms, only a 2.9 percentage point shortening of the lower CI and a 1.6 percentage point shortening of the upper CI. According to the Applicant, the estimated duration for the proposed study with 50 patients treated with imlifidase plus 100 patients in the concurrent reference cohort is 3-4 years. The Applicant estimates that the study duration for a study with 75+150 patients would be 5-6 years. It is agreed by the CHMP that the benefit with a narrower confidence interval does not outweigh the disadvantages of a longer study as a condition for a full marketing authorisation. The proposed sample size (N=50) is therefore agreed by CHMP.

Experts considered the historical control group unsuitable since, although immunosuppressive treatment has not changed for the past 10 years, practice has changed and the understanding of the role of HLA immunization and the availability of single antigen bead assays. In addition, only limited information would be available from historical control patients. The experts were in favour of recruiting 1-2 concurrent control patients for each imlifidase treated patient from the same PAES site to address differences in site-specific practices and experience. Recommendation was given to adjust the protocol for local inclusion criteria. The Applicant agreed to include 1-2 site-matched control patients for each imlifidase-treated patient and to match the groups as far as possible. The applicant agreed to match imlifidase patients to concurrent reference cohort patients as far as possible. However, the Applicant emphasises that, regardless of the number of other factors one attempts to match between imlifidase-

treated vs concurrent control patients, these two groups will remain non-comparable in terms of long-term outcome due to confounding by level of sensitization. This is agreed by CHMP. The control group will be used to contextualize the study results. The study outcomes will still be highly important and meaningful.

Cell based CDCXM testing against the donor should be performed, whenever possible.

Upon request by CHMP, the applicant agreed to implement clinically relevant efficacy endpoints, ie. graft survival time (1 year after transplantation=primary analysis endpoint) and renal function after transplantation as important clinical outcomes.

*Additional post marketing data*

Patients will be observed over a period of 5 years in an extension study. This study is required under Article 9(4)(cc) of Regulation 726/2004 and Article 1(1)(a) and 1(2)(d) of Regulation 357/2014 to address concerns with a potential lack of efficacy in the long term due to the high rate of AMR in the target population that raises concerns with respect to the maintenance of a positive benefit-risk balance of the medicinal product.

The Applicant commits to submit the results of the planned FDA study to EMA.

## 2.5.4. Conclusions on the clinical efficacy

Imlifidase at a dose of 25 mg/kg, given once or twice, has been shown to be effective in cleaving essentially all IgG-antibodies, thereby leading to crossmatch conversion in highly sensitized patients with end-stage chronic kidney disease with the possibility of a subsequent kidney transplantation. The short-term (6 month) pooled data from **studies 02, 03, 04 and 06** and the very limited longer-term data from the ongoing study 14 regarding graft survival and function are encouraging.

Thus, the available efficacy data support a conditional marketing authorisation for Idefirix in the following therapeutic indication:

*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.*

However, the available information on the long-term graft functioning and survival is limited, which are relevant parts of the assessment of the efficacy of Idefirix in view of the scarcity of donated organs. In this sense, additional and longer term (1-year) efficacy data are required to provide comprehensive data. The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to confirm the long-term efficacy of Idefirix in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor, the MAH should submit the results of a prospective, observational long-term follow-up study to evaluate the long-term graft survival in patients treated with Idefirix prior to kidney transplantation (study 17-HMedIdeS-14).

- In order to confirm the long-term efficacy and safety of Idefirix in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor, the MAH should conduct and submit the results of a controlled, open-label study investigating 1-year graft survival rate in kidney transplant patients with positive crossmatch against a deceased donor after desensitisation with Idefirix (study 20-HMedIdeS-19).

In addition, higher rate of AMR reported in the target population could have an impact on long-term outcome since episodes of AMR are considered a risk factor for shorter graft survival. The CHMP considers the following measures necessary to address issues related to efficacy:

- In order to further investigate the long-term graft survival in patients who have undergone kidney transplantation after Idefirix administration, the MAH should conduct and submit the results of a prospective 5-year-extension observational follow-up study. This study is a condition for the marketing authorisation and is necessary under Article 9(4)(cc) of Regulation 726/2004 and Article 1(1)(a) and 1(2)(d) of Regulation 357/2014 to address concerns with a potential lack of efficacy in the long term with respect to the maintenance of a positive benefit-risk balance, and which can only be resolved after the product has been authorised.

## *2.6. Clinical safety*

At the cut-off date of 01 December 2018, a total of 88 subjects were administered imlifidase process 1, including highly sensitized subjects with end-stage CKD, who were waiting for renal transplantation (54), healthy subjects (20), as well as subjects treated with imlifidase for other indications (9) and patients treated on a named-patient basis (5). Concerning Process 2 material a Phase I study, 18-HMedIdeS-15 (Study 15), has been conducted meanwhile, evaluating safety and tolerability, pharmacokinetics, and pharmacodynamics of the drug product intended for commercialisation (Process 2). This was a placebo-controlled, double-blind, randomised study in healthy men at a single centre, randomising 20 healthy men aged 18 to 55 years to imlifidase (n=15) or placebo (n=5). Results from this study were submitted during the evaluation procedure.

Safety data in the target population with CKD is limited, stemming from studies 02, 03, 04 and the main study 06. It should also be emphasized that imlifidase is administered in a clinical setting where the underlying disease, immunosuppressive treatment, hospitalization, and the transplantation itself could give rise to a wide variety of safety issues.

Based on the mode of action, the best prediction of the adverse effect profile of imlifidase is to assume that the effect of the treatment is likely to resemble the clinical picture of IgG deficiency.

Clinical safety data were collected to include standard reporting of AEs, SAEs, vital signs, ECGs and other laboratory data.

Additional safety assessments were done by organ system or syndrome and included, infections, infusion-related reactions, serum sickness, immunogenicity – Development of ADAs and interactions, e.g. with IVIg.

Across the Safety Analysis Set (SAS) of 54 patients with CKD (27 men and 27 women) the mean age was 43.8 years (range: 20 to 73 years).

**Exposure relevant for safety evaluation**

$C_{max}$ of imlifidase was observed at or soon after the end of the infusion, with a mean of 6.0 (4.4-7.5) µg/mL after a dose of 0.25 mg/kg. The AUC of imlifidase was determined to a mean of 202 (69-1010) hr*µg/mL after a dose of 0.25 mg/kg.

## *Patient exposure*

Of the 54 patients (SAS) exposed to imlifidase, 46 were transplanted afterwards (1 dose: n=42; 2 doses: n=4) and 8 were non-transplanted (1 dose: n=4; 2 doses: n=4).

**Table 51 Disposition (safety set)**

| | Study 02 | Study 03 | Study 04 | Study 06 | Total |
|---|---|---|---|---|---|
| No. of treated subjects | 8 | 10 | 17 | 19 | 54 |
| No. of transplanted subjects | 1 (12.5) | 10 (100.0) | 17 (100.0) | 18 (94.7) | 46 (85.2) |
| No. of not transplanted subjects | 7 (87.5) | | | 1 (5.3) | 8 (14.8) |
| According to protocol | 7 (87.5) | | | | 7 (13.0) |
| Adverse event | | | | 1 (5.3) | 1 (1.9) |
| No. of subjects completed core study | 8 (100.0) | 10 (100.0) | 15 (88.2) | 16 (84.2) | 49 (90.7) |
| No. of subjects with drug withdrawal/interruption | 1 (12.5) | | | 3 (15.8) | 4 (7.4) |
| No. of subjects discontinued study | | | 2 (11.8) | 3 (15.8) | 5 (9.3) |
| Adverse event | | | | 1 (5.3) | 1 (1.9) |
| Lost to follow-up | | | 1 (5.9) | | 1 (1.9) |
| Other | | | | 1 (5.3) | 1 (1.9) |
| Withdrawal by subject | | | 1 (5.9) | 1 (5.3) | 2 (3.7) |

One subject was included in 2 studies (Study 02 and Study 03). Due to the long time-period between the participation in the 2 studies (1.5years), this subject is treated as 2 subjects, 1 in each study.

The target dose for imlifidase for MA is one dose with 0.25 mg/kg. 46 of the 54 patients with CKD (85%) received a single dose of imlifidase (41 with a single dose of 0.25 mg/kg, 5 with 0.50 mg/kg) and 8 (15%) received 2 doses (5 with 2 doses of 0.12 mg/kg, 5 with 2 doses of 0.25 mg/kg). The maximum dose administered was 0.50 mg/kg (n=10).

35 subjects were followed for at least 1 year in study 14, 20 subjects for 3 years and 1 subject for 3-5 years (data cut-off 30-Sep-2019). Further long-term safety data is missing currently.

Five subjects with CKD discontinued treatment (5/54; 9%). Reasons for study discontinuation included withdrawal by subject (n=2), AE (n=1), lost to follow-up (n=1) and other (n=1).

Not all transplanted patients (17,4%) in the studies were highly sensitized (**Table 52**).

15,2% (n=7 patients) of the patients were flow cytometry crossmatch (FCXM) negative and 23.9% (n=11 patients) complement-dependent cytotoxicity cross-match (CDCXM) negative (both for B- and T-cells) (**Table 53**).

**Table 52 cPRA at Baseline (safety set; transplanted)**

| | | **Total (N=46)** |
|---|---|---|
| cPRA (%) MFI cut-off 2000 | n | 46 |
| | Mean (SD) | 89.326 (18.879) |
| | Median | 98.390 |
| | Min; Max | 21.82; 100.00 |
| | Under 80% | 8 (17.4) |
| | 80-95% | 8 (17.4) |
| | 95-98% | 5 (10.9) |
| | 98% (97.51-98.50) | 2 (4.3) |
| | 99% (98.51-99.50) | 3 (6.5) |
| | 100% (99.51-100) | 20 (43.5) |

**Table 53 Crossmatch, pre-dose (safety set, transplanted)**

| | | | T-cells | | | |
|---|---|---|---|---|---|---|
| Crossmatch | | | Negative | Positive | Missing | Total |
| FCXM | B-cells | Negative | 7 (15.2%) | 2 (4.3%) | | 9 (19.6%) |
| | | Positive | 22 (47.8%) | 14 (30.4%) | | 36 (78.3%) |
| | | Missing | | 1 (2.2%) | | 1 (2.2%) |
| CDCXM | B-cells | Negative | 11 (23.9%) | | | 11 (23.9%) |
| | | Positive | 7 (15.2%) | 3 (6.5%) | | 10 (21.7%) |
| | | Missing | 2 (4.3%) | | 23 (50.0%) | 25 (54.3%) |

## *Adverse events*

Treatment-emergent AEs were defined as AEs occurring after the start of the IMP infusion and within 30 days after the last infusion was stopped.

A posttreatment-emergent AE was any AE occurring after the time of the residual drug effect of the IMP, i.e. > 30 days after stop of the last imlifidase infusion. The focus of the assessment of safety will be on TEAEs, since posttreatment-emergent AEs occurred at a timepoint where the pharmacological effect of imlifidase is considered negligible.

All 54 patients (100%) of the SAS with CKD had at least one AE and 19 patients (35%) experienced at least 1 AE that was suspected to be related to imlifidase. Severe treatment-emergent non-SAEs were reported by 25 patients with CKD (46%). Three of those events (6%) were classified as related (**Table 54**).

**Table 54 Summary of AEs, by total dose (safety set)**

| | No. of Subjects (% of Subjects) and No. of Events | | |
|---|---|---|---|
| | 0.25 mg/kg (N=44) | 0.50 mg/kg (N=10) | Total (N=54) |
| Subjects with at least one AE | 44 (100.0) 626 | 10 (100.0) 139 | 54 (100.0) 765 |
| Subjects with at least one TEAE | 44 (100.0) 409 | 10 (100.0) 76 | 54 (100.0) 485 |
| Subjects with at least one related AE | 14 (31.8) 36 | 6 (60.0) 12 | 20 (37.0) 48 |
| Subjects with at least one related TEAE | 14 (31.8) 33 | 5 (50.0) 11 | 19 (35.2) 44 |
| Subjects with at least one TEAE, leading to study discontinuation | 1 (2.3) | 0 | 1 (1.9) |
| Subjects with at least one TEAE, leading to treatment discontinuation | 2 (4.5) 7 | 0 | 2 (3.7) 7 |
| Subjects with severe treatment-emergent non-SAEs | 19 (43.2) 36 | 6 (60.0) 17 | 25 (46.3) 53 |
| Subjects with severe related treatment-emergent non-SAEs | 2 (4.5) 3 | 1 (10.0) 1 | 3 (5.6) 4 |
| Subjects with a fatal AE | 0 | 0 | 0 |
| Subjects with a not recovered TEAE | 12 (27.3) 28 | 8 (80.0) 14 | 20 (37.0) 42 |
| Subjects with a recovering TEAE | 3 (6.8) 5 | 0 | 3 (5.6) 5 |
| Subjects with a TEAE recovered with sequelae | 1 (2.3) 1 | 0 | 1 (1.9) 1 |
| Subjects with a recovered TEAE | 44 (100.0) 372 | 10 (100.0) 61 | 54 (100.0) 433 |
| Subjects with a TEAE of unknown outcome | 3 (6.8) 3 | 1 (10.0) 1 | 4 (7.4) 4 |

**Treatment-related treatment emergent adverse events**

Relationship assessments of all AEs were done by the investigator based on the temporal relationship or mode of action of imlifidase, i.e. depletion of the IgG pool.

**Table 55** summarizes the number of subjects with TEAEs suspected by the investigator of being treatment-related.

**Table 55 Related AEs by CTC/intensity (safety set)**

| | | No. of Subjects (% of Subjects) | |
|---|---|---|---|
| | CTC/Intensity | Transplanted (N=46) | Not transplanted (N=8) |
| Subjects with any AE; maximum intensity | Mild | 3 (6.5) | 3 (37.5) |
| | Moderate | 3 (6.5) | 1 (12.5) |
| | Severe | 5 (10.9) | 3 (37.5) |
| | Life-threatening | 2 (4.3) | 0 |
| | Fatal | 0 | 0 |

**Table 56** summarizes the number of subjects with TEAEs and post-TEAEs suspected by the investigator of being treatment related.

**Table 56 Related TEAEs and related post-TEAEs by PT (safety set)**

| | No. of Subjects (% of Subjects) and No. of Events | | |
|---|---|---|---|
| | TEAE (N=54) | Post-TEAE (N=54) | Total (N=54) |
| Total | 19 (35.2) 44 | 4 (7.4) 4 | 20 (37.0) 48 |
| Aspartate aminotransferase increased | 2 (3.7) 3 | | 2 (3.7) 3 |
| Headache | 2 (3.7) 3 | | 2 (3.7) 3 |
| Pneumonia | 1 (1.9) 1 | 2 (3.7) 2 | 3 (5.6) 3 |
| Urinary tract infection | 3 (5.6) 3 | | 3 (5.6) 3 |
| Alanine aminotransferase increased | 2 (3.7) 2 | | 2 (3.7) 2 |
| Dizziness postural | 1 (1.9) 2 | | 1 (1.9) 2 |
| Flushing | 2 (3.7) 2 | | 2 (3.7) 2 |
| Infusion related reaction | 2 (3.7) 2 | | 2 (3.7) 2 |
| Infusion site pain | 2 (3.7) 2 | | 2 (3.7) 2 |
| Myalgia | 2 (3.7) 2 | | 2 (3.7) 2 |
| Sepsis | 2 (3.7) 2 | | 2 (3.7) 2 |
| Abdominal infection | | 1 (1.9) 1 | 1 (1.9) 1 |
| Adenovirus infection | 1 (1.9) 1 | | 1 (1.9) 1 |
| Anaemia | 1 (1.9) 1 | | 1 (1.9) 1 |
| Blood phosphorus increased | 1 (1.9) 1 | | 1 (1.9) 1 |
| Blood triglycerides increased | 1 (1.9) 1 | | 1 (1.9) 1 |
| Catheter site infection | 1 (1.9) 1 | | 1 (1.9) 1 |
| Dyspnoea | 1 (1.9) 1 | | 1 (1.9) 1 |
| Escherichia test positive | 1 (1.9) 1 | | 1 (1.9) 1 |
| Feeling hot | 1 (1.9) 1 | | 1 (1.9) 1 |
| Hypertension | 1 (1.9) 1 | | 1 (1.9) 1 |
| Hypotension | 1 (1.9) 1 | | 1 (1.9) 1 |
| Infection | 1 (1.9) 1 | | 1 (1.9) 1 |

| | No. of Subjects (% of Subjects) and No. of Events | | |
|---|---|---|---|
| | TEAE (N=54) | Post-TEAE (N=54) | Total (N=54) |
| Influenza | 1 (1.9) 1 | | 1 (1.9) 1 |
| Parvovirus infection | | 1 (1.9) 1 | 1 (1.9) 1 |
| Postoperative wound infection | 1 (1.9) 1 | | 1 (1.9) 1 |
| Rash | 1 (1.9) 1 | | 1 (1.9) 1 |
| Scleral haemorrhage | 1 (1.9) 1 | | 1 (1.9) 1 |
| Sinus tachycardia | 1 (1.9) 1 | | 1 (1.9) 1 |
| Transplant rejection | 1 (1.9) 1 | | 1 (1.9) 1 |
| Upper respiratory tract infection | 1 (1.9) 1 | | 1 (1.9) 1 |
| Visual impairment | 1 (1.9) 1 | | 1 (1.9) 1 |
| Wound infection | 1 (1.9) 1 | | 1 (1.9) 1 |

In transplanted patients, the most commonly reported preferred terms (PTs) of severe intensity (at least 5% of transplanted patients) were transplant rejection (10 patients [22%]), anaemia and hypophosphataemia (4 patients [9%] each), and delayed graft function, hyperkalaemia and hypomagnesaemia (3 patients [7%] each). There was a trend of severe TEAEs being more common in patients receiving a total dose of 0.50 mg/kg than in those receiving 0.25 mg/kg, **Table 57**.

**Table 57 Severe TEAEs by total dose and preferred term (PT), occurring in at least 5% of subjects (safety set, transplanted)**

| | No. of Subjects (% of Subjects) and No. of Events | | |
|---|---|---|---|
| | 0.25 mg/kg (N=38) | 0.50 mg/kg (N=8) | Total (N=46) |
| Total | 20 (52.6) 50 | 7 (87.5) 23 | 27 (58.7) 73 |
| Transplant rejection | 5 (13.2) 6 | 5 (62.5) 6 | 10 (21.7) 12 |
| Anaemia | 2 (5.3) 2 | 2 (25.0 ) 2 | 4 (8.7) 4 |
| Hypophosphataemia | 3 (7.9) 3 | 1 (12.5) 1 | 4 (8.7) 4 |
| Delayed graft function | 2 (5.3) 2 | 1 (12.5) 1 | 3 (6.5) 3 |
| Hyperkalaemia | 3 (7.9) 3 | | 3 (6.5) 3 |
| Hypomagnesaemia | 2 (5.3) 2 | 1 (12.5) 1 | 3 (6.5) 3 |

**Averse events of special interest**

Potential adverse events of special interest (AESIs) were pre-defined in the SAP: severe or serious infections, infusion-related reactions, myalgia and serum sickness.

*Severe or serious infections*

Based on the imlifidase mode-of-action, there is potentially an increased risk of *severe or serious infections* when IgG levels are compromised. IgG levels start, according to the applicant, to return 1-2 weeks after treatment with imlifidase but may be suppressed up to approximately 1 month or until IVIg is administered.

Severe or serious infections were reported at a higher frequency in patients receiving a total imlifidase dose of 0.50 mg/kg.

**Table 58** presents severe or serious infections assessed as related to imlifidase.

**Table 58 Related potential AESIs within the AESI 'Severe or serious infections' by PT and subpopulation (Safety set + HV)**

| | | No. of Subjects (% of Subjects) and No. of Events | | | |
|---|---|---|---|---|---|
| | | Transplanted (N=46) | Not transplanted (N=8) | HV-imlifidase (N=20) | HV-Placebo (N=9) |
| Severe or Serious Infections | Total | 7 (15.2) 9 | 2 (25.0) 2 | 0 | 0 |
| | Abdominal infection | 1 (2.2) 1 | | | |
| | Catheter site infection | 1 (2.2) 1 | | | |
| | Infection | 1 (2.2) 1 | | | |
| | Parvovirus infection | 1 (2.2) 1 | | | |
| | Pneumonia | 2 (4.3) 2 | 1 (12.5) 1 | | |
| | Sepsis | 2 (4.3) 2 | | | |
| | Upper respiratory tract infection | | 1 (12.5) 1 | | |
| | Urinary tract infection | 1 (2.2) 1 | | | |

9 of the 74 subjects (12%) exposed to imlifidase had at least 1 related AE within the potential AESI of 'Severe or serious infections', of whom 2 patients were not transplanted (transplantation was not planned in accordance with the study protocol)

*Infusion-related reactions*

As for other biologic agents administered IV, *infusion-related reactions* may occur during imlifidase infusion. All AESIs of 'Infusion-related reaction' were reported in patients receiving a total imlifidase dose of 0.25 mg/kg. **Table 59** presents Related potential AESIs within the AESI 'infusion-related reactions.

**Table 59 Related potential AESIs within the AESI 'infusion-related reactions' by PT and subpopulation (Safety set + HV)**

| | No. of Subjects (% of Subjects) and No. of Events | | | |
|---|---|---|---|---|
| | Transplanted (N=46) | Not Transplanted (N=8) | HV-imlifidase (N=20) | HV-placebo (N=9) |
| Total | 1 (2.2) 1 | 2 (25.0) 3 | 1 (5.0) 3 | 1 (11.1) 1 |
| Chest discomfort | | | 1 (5.0) 1 | |
| Dyspnoea | | 1 (12.5) 1 | | |
| Flushing | | 1 (12.5) 1 | 1 (5.0) 1 | |
| Infusion related reaction | 1 (2.2) 1 | 1 (12.5) 1 | | 1 (11.1) 1 |
| Pharyngeal oedema | | | 1 (5.0) 1 | |

*Serum sickness*

Serum sickness is a type III hypersensitivity reaction that results from the injection of heterologous or foreign protein or serum, leading to the development of antibodies against the foreign molecule and the formation of immune complexes. Serum sickness was observed only in studies with TTP patients, indication in which the development is no longer pursued as declared by the applicant.

No patient with CKD experienced serum sickness.

*Myalgia*

Myalgia has been reported during treatment with other biologics such as IVIg and rituximab.

One of the 54 patients (2%) with CKD experienced 'severe or serious myalgia' 2 days after the second dose of 0.25 mg/kg imlifidase, which did not resolve during the study. This patient had previously reported myalgia due to atorvastatin, and the event was assessed as related to imlifidase.

**Transplantation-related Outcomes**

According to the applicant, *Delayed Graft Function* (DGF), which represents a suboptimal renal function immediately following kidney transplantation, is a manifestation of acute kidney injury and is defined as the need for dialysis within 7 days of transplantation.

DGF was reported as an AE in 6 patients, none of which was considered related to imlifidase.

*Graft loss*

Graft loss occurred in 3 of the 46 transplanted patients (7%) including 1 patient (2%) who experienced an IgM-mediated hyperacute rejection (HAR) starting immediately after transplantation (-one subject no DSA or HLA antibodies in serum, not related to imlifidase).

*Antibody-mediated rejection (AMR)*

Eleven of the 46 transplanted patients (24%) had a biopsy-proven or presumed AMR. A total of 15 of 46 patients (33%) had any antibody-mediated change. One transplant rejection (SAE) was assessed as related to imlifidase.

Two of the 11 patients with AMR (18%) received 2 doses of imlifidase vs 2 of the 35 patients (6%) without any AMR.

Eight of the 14 patients (57%) with a pre-treatment FCXM status of B+/T+ had an AMR, whereof 6 patients had an active AMR and 2 patients had a mixed AMR/CMR. As a comparison, none of the 7 patients with a pre-treatment FCXM status of B-/T- had an AMR.

Of the 7 patients with a pre-treatment CDCXM status of B+/T-, 2 patients (29%) had an active AMR, while 5 patients had no active AMR, mixed AMR/CMR or presumed AMR. Of the 11 patients with a pre-treatment CDCXM status of B-/T-, 1 patient (9%) had an active AMR and 1 patient (9%) had a mixed AMR/CMR.

The percentage of patients with at least 1 related AE was almost identical in patients with biopsy-proven or presumed AMR (3 of 11 patients [27%]) and those without any such event (10 of 35 patients [29%]). One of 11 patients (9%) with biopsy-proven or presumed AMR vs 6 of 35 patients (17%) without such events had at least 1 related SAE.

The 4 related AEs occurring in the 3 patients with biopsy-proven or presumed AMR included 1 AE each of adenovirus infection, infection, rash and transplant rejection, whereof the event of transplant rejection was serious.

Serious potential AESIs (all of which were serious infections) occurred in 6 of 11 patients (55%) with biopsy-proven or presumed AMR and in 13 of 35 patients (37%) without such events.

## *Serious adverse event/deaths/other significant events*

**Serious adverse events**

A total of 112 SAEs were reported by 38 of the 54 patients (70%) with CKD. 20 % of the patients with CKD had 12 related SAEs, mostly infections (9 of the 12 related SAEs) including sepsis, but also infusion related reaction, myalgia and transplant rejection.

SAEs were reported at a higher frequency among patients receiving a total dose of 0.50 mg/kg (9 of 10 patients [90%]) than among those receiving a total dose of 0.25 mg/kg (21 of 44 patients [48%])(**Table 60**). This trend was observed also for related SAEs (**Table 61**).

**Table 60 Summary of SAEs, by total dose (safety set)**

| | No. of Subjects (% of Subjects) and No. of Events | | |
|---|---|---|---|
| | 0.25 mg/kg (N=44) | 0.50 mg/kg (N=10) | Total (N=54) |
| Subjects with at least one SAE | 28 (63.6) 84 | 10 (100.0) 28 | 38 (70.4) 112 |
| Subjects with at least one TESAE | 21 (47.7) 34 | 9 (90.0) 13 | 30 (55.6) 47 |
| Subjects with at least one related SAE | 7 (15.9) 8 | 4 (40.0) 4 | 11 (20.4) 12 |
| Subjects with at least one related TESAE | 5 (11.4) 5 | 3 (30.0) 3 | 8 (14.8) 8 |
| Subjects with at least one TESAE, leading to treatment discontinuation | 1 (2.3) 1 | 0 | 1 (1.9) 1 |
| Subjects with severe TESAEs | 12 (27.3) 16 | 8 (80.0) 9 | 20 (37.0) 25 |
| Subjects with severe related TESAEs | 3 (6.8) 3 | 3 (30.0) 3 | 6 (11.1) 6 |
| Subjects with a fatal SAE | 0 | 0 | 0 |
| Subjects with a not recovered TESAE | 1 (2.3) 1 | 1 (10.0) 1 | 2 (3.7) 2 |
| Subjects with a recovered TESAE | 20 (45.5) 33 | 8 (80.0) 12 | 28 (51.9) 45 |

Overall, the most commonly reported SAEs were transplant rejection reported by 19 patients (35%), and urinary tract infection and increased blood creatinine (5 patients [9%] each). shows SAEs reported by at least 2 patients with CKD.

**Table 61 Related SAEs and event rates, by SOC and PT (safety set)**

| | | 0.25 mg/kg (N=44) | | 0.50 mg/kg (N=10) | | Total (N=54) | |
|---|---|---|---|---|---|---|---|
| | | n (%) events | Event rate (per 100-subject-years) | n (%) events | Event rate (per 100-subject-years) | n (%) events | Event rate (per 100-subject-years) |
| Time at risk (years) | | | 18.7 | | 4.4 | | 23.1 |
| Total | | 7 (15.9) 8 | 42.7 | 4 (40.0) 4 | 91.1 | 11 (20.4) 12 | 51.9 |
| Infections and infestations | Subjects | 5 (11.4)6 | 32.0 | 3 (30.0)3 | 68.3 | 8 (14.8)9 | 38.9 |
| | Abdominal infection | 1 (2.3) 1 | 5.3 | | | 1 (1.9) 1 | 4.3 |
| | Catheter site infection | 1 (2.3) 1 | 5.3 | | | 1 (1.9) 1 | 4.3 |

| | | 0.25 mg/kg (N=44) | | 0.50 mg/kg (N=10) | | Total (N=54) | |
|---|---|---|---|---|---|---|---|
| | | n (%) events | Event rate (per 100-subject-years) | n (%) events | Event rate (per 100-subject-years) | n (%) events | Event rate (per 100-subject-years) |
| | Parvovirus infection | | | 1 (10.0) 1 | 22.8 | 1 (1.9) 1 | 4.3 |
| | Pneumonia | 2 (4.5) 2 | 10.7 | 1 (10.0) 1 | 22.8 | 3 (5.6) 3 | 13.0 |
| | Sepsis | 1 (2.3) 1 | 5.3 | 1 (10.0) 1 | 22.8 | 2 (3.7) 2 | 8.7 |
| | Upper respiratory tract infection | 1 (2.3) 1 | 5.3 | | | 1 (1.9) 1 | 4.3 |
| Immune system disorders | Subjects | 1 (2.3)1 | 5.3 | | | 1 (1.9)1 | 4.3 |
| | Transplant rejection | 1 (2.3) 1 | 5.3 | | | 1 (1.9) 1 | 4.3 |
| Musculoskeletal and connective tissue disorders | Subjects | | | 1 (10.0)1 | 22.8 | 1 (1.9)1 | 4.3 |
| | Myalgia | | | 1 (10.0) 1 | 22.8 | 1 (1.9) 1 | 4.3 |
| Injury, poisoning and procedural complications | Subjects | 1 (2.3)1 | 5.3 | | | 1 (1.9)1 | 4.3 |
| | Infusion related reaction | 1 (2.3) 1 | 5.3 | | | 1 (1.9) 1 | 4.3 |

**Deaths**

No deaths were reported in the studies 02, 03, 04 or 06. Three deaths have occurred so far in imlifidase treated patients (study 14). The deaths occurred 7, 10.5 and 12 months after a single treatment. The causes of these late occurring deaths (circulatory arrest, unknown cause and *Pseudomonas Bacteraemia*) do not implicate a direct involvement of imlifidase.

## *Laboratory findings*

Abnormal laboratory values were observed in patients with CKD, with the overall pattern of the abnormalities consistent with the expected pattern in this patient population.

Although a number of patients had an elevated liver enzyme at least once after imlifidase administration, no subjects fulfilled the criteria for Hy's law. 27 of 41 transplanted (and two of 8 non-transplanted) patients with any post-baseline ALT value and with a normal ALT baseline value had at least 1 ALT value above normal range over the 6-month study duration. 25 of 35 transplanted (and two of 7 non-transplanted) patients with a normal AST baseline value and 4 of 6 transplanted patients with a low AST baseline value had at least 1 AST value above normal range over the 6-month study duration.

Anaemia was reported as treatment related TEAE in 1 transplanted patient (1,9%).

## *Safety in special populations*

Imlifidase is recommended for use in adults. Only two transplanted subjects were >64 years old, therefore no conclusions can be drawn for the older patient population. No children or adolescents have been included in the clinical study programme.

**Elderly patients**

Five AEs reported in 3 patients aged ≥ 65 years were assessed as possibly related to imlifidase:

- one SAE of sepsis
- 4 non-serious AEs (flushing, infusion site pain, adenovirus infection and infection)

Except for 1 non-serious AE of adenovirus of moderate intensity, for which the outcome is unknown, related AEs in elderly patients resolved without sequelae.

**AEs by Presence of Hepatic Disease**

No patients with hepatic impairment have been investigated systematically yet.

Two patients presented hepatic disease (multiple benign hepatic cysts in combination with polycystic kidney disease; lupus hepatitis).

- One patient experienced multiple benign hepatic cysts in combination with polycystic kidney disease. This patient presented 6 non-serious AEs (anaemia, leukopenia, pyrexia, pain, lymphocele and transplant rejection), none of which was related to imlifidase and 4 SAEs (suspected infection, increased creatinine, parvovirus infection and transplant rejection), whereof 1 (parvovirus infection) was assessed as possibly related to the IMP. The transplant rejection (of moderate intensity and assessed as unlikely related) was adjudicated to be a CMR and resolved after 8 days.
- A second patient experienced lupus hepatitis. This patient presented 7 non-serious AEs (pain, pruritus, hypokalaemia, hypertension, chest discomfort, sepsis and dysuria), none of which was related to the IMP. No SAEs were reported.

**AEs by Presence of Diabetes**

Three of 8 transplanted patients with diabetes reported a total of 5 related AEs; 1 such AE each of adenovirus infection, anaemia, hypotension, infection and urinary tract infection i.e. the nature of AEs in patients with diabetes was similar to that of the total patient population. No patients with diabetes had any related SAE.

**AEs by Presence of Autoimmune Disease**

Three of 17 transplanted patients with autoimmune disease reported a total of 7 related AEs including abdominal infection, anaemia, catheter site infection, Escherichia test positive, pneumonia, postoperative wound infection and urinary tract infection, i.e. the nature of AEs in patients with autoimmune disease was similar to that of the total patient population. Three of the related AEs in patients with autoimmune disease were serious (1 each of abdominal infection, catheter site infection and pneumonia).

## *Immunological events*

ADAs against imlifidase have been observed after repeated dosing in nonclinical studies. According to the applicant, a total dose of 0.25 mg/kg was an inducer of ADA IgG as strong as 0.50 mg/kg.

### *Safety related to drug-drug interactions and other interactions*

Imlifidase is not expected to interact with the CYP450 drug metabolism system. However, being a potent IgG cleaving enzyme, therapeutic compounds containing IgG are susceptible to cleavage by imlifidase. Imlifidase cleaved some antibody-based therapeutics like basiliximab, rituximab, alemtuzumab, adalimumab, denosumab, belatacept, etanercept, rabbit anti-thymocyte globulin and IVIg.

No AEs relating to drug interactions occurred in the clinical programme.

Imlifidase does not degrade equine anti-thymocyte globulin (ATGAM).

### *Discontinuation due to adverse events*

Two patients discontinued treatment due to an AE. One patient was withdrawn from the study due to a related SAE (infusion related allergic reaction), one patient had the infusion discontinued due to non-serious, related AEs.

The infusion was temporarily interrupted in 2 patients due to infusion-related reactions (an AE and a SAE, respectively).

## 2.6.1. Discussion on clinical safety

At the cut-off date of 01 December 2018, a total of 88 subjects were administered imlifidase process 1, considering subjects treated with imlifidase within the clinical development programme for desensitizing subjects with CKD, who are scheduled for renal transplantation (20 healthy volunteers, 54 patients with CKD), as well as subjects treated with imlifidase for other indications (9) and patients treated on a named-patient basis (5).

Due to the proposed indication in patients with CKD, safety data of the studies in other indications (15-HMedIdeS-08, 15-HMedIdeS-10) and in HV (11-HMedIdeS-01 - Study 01) have not been analysed in detail. So the assessment of the safety profile of imlifidase in the claimed indication (desensitization treatment of highly sensitized adult kidney transplant patients with positive cross-match against an available deceased donor) is mainly based on data from 4 completed clinical studies in patients with CKD (Studies 02 - 13-HMedIdeS-02, 03 - 13-HMedIdeS-03, 04 - 14-HMedIdeS-04 and 06 - 15-HMedIdeS-06=safety set). The study data have a cut-off date of 01 Dec 2018.

Clinical safety data included standard reporting of AEs, SAEs, vital signs, ECGs and other laboratory data. Additional safety assessments were done by organ system or syndrome and included evaluation of infections, infusion-related reactions, serum sickness, immunogenicity – development of Anti-Drug Antibodies (ADAs) and interactions, e.g. with IVIg.

All relevant safety studies in humans were performed with process 1 material. The safety data of process 2 material from a study at a single centre, randomising 20 healthy men aged 18 to 55 years to imlifidase (n=15) or placebo (n=5), are comparable with safety data of process 1 material.

Across the Safety Analysis Set (SAS) of 54 patients with CKD (27 men and 27 women) the mean age was 43.8 years (range: 20 to 73 years). The clinical situation for intended use, i.e the kidney transplantation itself and concurrent immunosuppressive treatment is expected to generate a wide variety of AEs. The study population is very heterogeneous. This and the lack of a control group impair interpretation and causality assessment of AEs. Overall, in light of the rare claimed indication, observed demographics in the SAS are overall representative of the target population with the following exceptions.

The target dose of imlifidase for MA is one dose with 0.25 mg/kg. A second dose of 0.25 mg/kg can be administered if crossmatch conversion is not achieved after the 1st dose. 46 of the 54 patients with CKD (85%) received imlifidase (41 with a single dose of 0.25 mg/kg, 5 with 0.50 mg/kg) and 8 (15%) received 2 doses (5 with 2 doses of 0.12 mg/kg, 5 with 2 doses of 0.25 mg/kg). The maximum dose administered was 0.50 mg/kg (n=10).

35 of the 46 transplanted patients in studies 02, 03, 04, and 06 have been enrolled in the follow-up study 14. 35 subjects were followed for at least 1 year, 20 subjects for 3 years and one subject for 3-5 years (data cut-off 30-Sep-2019). Three deaths have occurred during the study, none of which were related to imlifidase. Three patients lost their graft after the end of the respective feeder study but prior to being enrolled in the study 14. The applicant proposed to investigate long-term safety in the ongoing Study 14 (17-HMedIdeS-14), in an observational registry and in a PAES study. Considering the rarity and severity of the disease and the high unmet medical in highly sensitized CKD waiting for a kidney transplant, and the fact that imlifidase is proposed to be given only once before transplantation or twice should crossmatch conversion not be achieved after the 1st dose, the limited premarketing data available is considered acceptable by CHMP.

Five subjects with CKD discontinued treatment (5/54; 9%). Reasons for study discontinuation included withdrawal by subject (n=2), AE (n=1), lost to follow-up (n=1) and other (n=1).

All 54 patients (100%) of the SAS with CKD had at least one AE and 19 patients (35%) experienced at least 1 AE that was suspected to be related to imlifidase. Severe treatment-emergent non-SAEs were reported by 25 patients with CKD (46%). Three patients had any related non-serious TEAE of severe intensity. Several AEs assessed as related to imlifidase by the investigator were, after thorough assessment of data, assessed as unrelated by the sponsor. The Applicant clarified that 3 non-serious TEAEs ('blood phosphorus increased', 'blood triglycerides increased' and 'Escherichia test positive'), reported in one patient each, assessed as related to imlifidase by the investigator were assessed as unrelated by the sponsor. Hyperphosphatemia is known to be associated with the underlying kidney disease (K/DOQI 2002; Zheng et al. 2011) and lipid abnormalities in ESRD are characterized by e.g. hypertriglyceridaemia (Vaziri et al. 2011). The positive Escherichia test was recorded in a patient with UTI which is associated with the total immunosuppressive treatment and has been reported to occur in > 30% of patients after kidney transplantation (Wu et al. 2016). The applicant did not propose these reactions in Section 4.8 of the proposed SmPC. However, it remains difficult to determine relatedness definitely due to a missing control arm in the studies in addition to the small database of only 54 patients with CKD treated with imlifidase for safety assessment. The Applicant revised the adverse reactions listed in the SmPC to include all AEs with at least a possible relationship to imlifidase, except for the two non-serious TEAEs of 'blood phosphorus increased' and 'blood triglycerides increased, as discussed above.

A total of 112 SAEs were reported by 38 of the 54 patients (70%) with CKD. 20 % of the patients with CKD had 12 related SAEs, mostly infections (9 of the 12 related SAEs) including sepsis, but also infusion related reaction, myalgia and transplant rejection. The applicant clarified that three deaths occurred so far in imlifidase treated patients. The deaths occurred 7, 10.5 and 12 months after a single treatment. At those timepoints, imlifidase would long have been cleared from the patients. The causes of these late occurring deaths (circulatory arrest, unknown cause and Pseudomonas Bacteraemia) do not implicate a direct involvement with imlifidase.

Related AEs (50% vs 32%) and SAEs (30% vs 11%) were reported at a higher frequency in patients receiving a total dose of 0.50 mg/kg than in those receiving a total dose of 0.25 mg/kg, respectively. Overall, the lowest incidence of related TEAEs was observed in patients receiving a single dose of 0.25 mg/kg (8 of 37 patients [22%]) and the highest in patients receiving 2 doses of 0.12 mg/kg (1 of 1 patient). Any differences across dosing regimens are likely to reflect the low number of patients

receiving dosing regimens other than a single dose of 0.25 mg/kg. No obvious differences in the nature of AEs were observed when comparing patients receiving a total imlifidase dose of 0.25 mg/kg with those receiving 0.50 mg/kg. However, due to only 10 patients having received the higher dose, interpretation is difficult. Across dosing regimens, the pattern of AEs was similar to that of kidney-transplanted patients not receiving imlifidase.

Relationship assessments of all AEs were done by the investigator based on the temporal relationship or mode of action of imlifidase, i.e. depletion of the IgG pool. The potential adverse events of special interest (AESIs, pre-defined in the SAP) were severe or serious infections, infusion-related reactions, serum sickness and myalgia.

*Severe or serious infections*

Based on imlifidase mode-of-action, there is potentially an increased risk of infections when IgG levels are compromised. IgG levels start to return 1-2 weeks after treatment with imlifidase but may be suppressed up to approximately 1 month or until IVIg is administered. Nine of the 54 subjects (17%) exposed to imlifidase had at least 1 related AE within the potential AESI of 'Severe or serious infections'; 7 of 46 transplanted patients with CKD (15%), 2 of 8 non-transplanted patients (25%). Related AEs (PTs) within this potential AESI that occurred in > 1 subject included pneumonia (3 patients) and sepsis (2 patients). The seven transplanted patients had any severe or serious infection occurring post-transplantation. In transplanted patients, no infections occurred pre-transplantation, which is consistent with kidney transplantations not being performed in patients having an ongoing infection. Severe or serious infections were reported at a higher frequency in patients receiving a total imlifidase dose of 0.50 mg/kg. To mitigate the risk of infections, prophylactic antibiotic was given until IVIg was administered or IgG returned to acceptable levels. Cases of infection occur despite prophylaxis also in the general transplantation setting. Compared with the standard of care after kidney transplantation in general, an oral antibiotic agent covering bacteria causing respiratory tract infections was added to reduce the potentially increased risk of such infections, as these are the most common in patients with hypogammaglobulinemia. Overall, the pattern of infections observed in transplanted patients after imlifidase treatment is consistent with the pattern of infections reported in patients not treated with imlifidase. The use of imlifidase is contraindicated in patients with ongoing serious infection (section 4.3 of the SmPC). In addition, an appropriate recommendation on prophylactic oral antibiotics is included in section 4.4. of the SmPC.

*Infusion-related reactions*

As for other biologic agents administered IV, infusion-related reactions may occur during imlifidase infusion. To mitigate the risk of infusion-related reactions, glucocorticoids and antihistamines were given prior to dosing. Five subjects had at least 1 related AE within the potential AESI 'Infusion-related reactions', including 3 of 54 patients with CKD. One of the 3 related infusion-related reactions in patients with CKD was serious and resulted in treatment and study discontinuation. Infusion-related reactions are common despite pre-treatment with antihistamine and/or corticosteroids after infusion of several biologics. The incidence of infusion-related reactions after premedication and imlifidase infusion was low compared with those of several other biologics. All 54 patients with CKD received prophylaxis, of whom 4 (7%) experienced an infusion-related reaction in association with imlifidase infusion. All AESIs of 'Infusion-related reaction' were reported in patients receiving a total imlifidase dose of 0.25 mg/kg. There were no indications that infusion-related reactions were dose-dependent. The Section 4.4 of the SmPC provides a recommendation as to when discontinue the infusion and when the infusion could be restarted following an infusion-related reaction.

*Serum sickness*

Serum sickness is a type III hypersensitivity reaction that results from the injection of heterologous or foreign protein or serum, leading to the development of antibodies against the foreign molecule and the formation of immune complexes. Serum sickness was observed in the studies with patients in the indication Thrombotic thrombocytopenic purpura (TTP). As indicated in the application, this indication is no longer pursued. The applicant has deleted serum sickness initially proposed in sections 4.4 and 4.8 since no cases of serum sickness have been observed in the clinical program for CKD patients. During imlifidase development, since 2/2 TTP patients developed serum sickness, the Applicant has included a contraindication in the section 4.3 of the SmPC for patients with TTP. This is endorsed by CHMP.

*Myalgia*

*Myalgia* has been reported during treatment with other biologics such as IVIg and rituximab. One of the 54 patients (2%) with CKD experienced 'severe or serious myalgia' 2 days after the second dose of 0.25 mg/kg imlifidase. The event was assessed as related to imlifidase. Myalgia should also be reported post-marketing in the PSUR.

Overall, the main safety concerns are infusion related reactions and infections, which are classified as important identified risks in the RMP.

*Transplantation related outcomes* reported were delayed graft function (DGF), graft loss and rejection episodes.

DGF was reported as an AE in 6 patients, none of which was considered related to imlifidase. From the data provided it could be concluded that the causes of DGF could be other than the administration of imlifidase (e.g. deceased donor, higher CIT).

Graft loss occurred in 3 of the 46 (7%) transplanted patients, which is within an acceptable range in comparison to the literature (5-7%)[3,4].

Eleven of the 46 transplanted patients (24%) had a biopsy-proven or presumed antibody-mediated rejection (AMR). A total of 15 of 46 patients (33%) had any antibody-mediated change. This seems to be high in comparison to the literature (8-20%)[5,6]. However, according to the applicant, the overall frequency of classic active biopsy-proven or presumed AMR of 24% after imlifidase treatment is within the frequency range reported for highly sensitized patients transplanted after various desensitization protocols. The aim of imlifidase is to desensitize patients to make them transplantable. In the three trials preceding **study 06**, i.e. **02, 03, 04**, not all patients needed to have "a" positive CXM at baseline. In the analysis of AMR (as a safety endpoint) by baseline positivity of CXM (FACS/FCXM and CDC), a lack of efficacy in terms of AMR was observed in patients baseline FXCM, and in particular CDCXM, positive.

In addition, one transplant rejection (SAE) was assessed as related to imlifidase (reappearance of DSA, which started to reappear at 48 hours after imlifidase treatment/lack of efficacy). It was not clear why transplant rejection in another subject was assessed as unrelated. It is not clear why transplant rejection in another subject was assessed as unrelated by the Investigator; however, longer time to the event, 5 days vs. 2 days, is noted. Both subjects were converted from crossmatch-positive to negative, demonstrating efficacy with respect to the purpose of imlifidase treatment, the difference

[3] Phelan PJ, O'Kelly P, Tarazi M, et al. Renal allograft loss in the first post-operative month: Causes and consequences. Clin Transplant 2012; 26: 544–549
[4] Khalkhali HR, Hajizadeh E, Kazemnejad A, Ghafari A (2010) Longterm progression pattern of chronic allograft dysfunction among kidney transplant recipients. Iran J Kidney Dis 4: 244.
[5] http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx
[6] Hart A, Smith JM, Skeans MA, Gustafson SK, Stewart DE, Cherikh WS, Wainright JL, Kucheryavaya A, Woodbury M, Snyder JJ, Kasiske BL, Israni AK Am J Transplant. 2017;17 Suppl 1:21

being the time to rebound of DSA. The basis for the causality determination of "possibly related" was due to lack of efficacy, or temporary efficacy, of the IMP, not implying that imlifidase itself was responsible for the rejection. The Applicant considers likely that the initial complete cleavage was followed by HLA antibody rebound when the imlifidase concentration decreased, so the event is not considered to be lack of efficacy. In conclusion, both transplant rejections don't seem to be a direct consequence of imlifidase treatment, but due to an anticipated rebound of DSA. This is agreed by CHMP.

*Laboratory changes* over time were consistent with the clinical features of CKD and transplantation. However, the magnitude of these effects cannot be contextualized, as the studies were uncontrolled. There are no clear indications that imlifidase is hepatotoxic or contributes to elevated liver enzymes in kidney-transplanted patients. There is currently no mechanistic rationale for hepatotoxicity. Elevated levels of liver enzymes could occur in patients who have undergone kidney transplantation since the procedure requires the use of several concomitant medications including immunosuppressive and antibiotic treatment with known potential to cause hepatotoxicity. The role of imlifidase in the occurrence of elevated liver enzymes remains unclear and no firm conclusions can be drawn from presented data. ALT and AST elevations are included as adverse drug reactions in the SmPC section 4.8

No dedicated studies were provided in *special populations*. Five AEs reported in 3 patients aged ≥ 65 years were assessed as possibly related to imlifidase. The mean age was higher in patients who received a total dose of 0.50 mg/kg. In summary, due to the small number of patients no relevant safety conclusions can be drawn with regard to special populations.

With regard to hepatic impairment as well as drug-drug interactions and the observation of ADAs after repeated dosing in nonclinical studies, the applicant presented limited information and data. There is no apparent dose-related difference in the post-treatment level of ADA between 2 doses. To the knowledge of the applicant, there is nothing in the literature that suggests that ADA are harmful *per se* or that they might cross-react with any autologous proteins. The increase in anti-imlifidase IgG seen in patients with CKD after imlifidase administration had no identified impact on the safety in the clinical programme. The recommendation to administer imlifidase 24 h prior to transplantation is based on cold ischemia time and the turn-around time of CXM results and not related to the reoccurrence of ADA. Based on the mode of action, there is no theoretical concern regarding the administration of a second imlifidase dose in case of re-transplantation. However, it is agreed that based on current knowledge it is not possible to provide any recommendations on this issue. Imlifidase is currently accepted for one-time use only (one or two doses within 24 hours).

The CHMP enquired on a potential risk associated with the cleavage mediated by imlifidase and a massive production of a fragment and dimeric Fc fragment in the intended patient population. According to the applicant there are indications, both in healthy and newly transplanted subjects, that imlifidase cleaved IgG fragments are renally cleared. Human IgG Fc MW is according to literature around 57 kDa and the F(ab')2 fragment 110 kDa. Kidney cut-off for protein excretion is ca 60 kDa. Thus, it is conceivable that without proteolysis the Fc fragment is excreted unchanged. No renal toxicity related to imlifidase has hitherto been observed. The issue was therefore not further pursued by CHMP.

The CHMP enquired about the potential for imlifidase to alter vaccination status. The applicant clarified that the antigen specific IgG started to increase again two to three days post treatment and the levels of antigen specific IgG then quickly increased in all test subjects to between approximately 60-80% of pre-treatment levels within the first four weeks. At day 63 (9 weeks) the antigen-specific IgG was totally restored in two of the subjects, whereas in the other two subjects about 70% of pre-treatment levels

were reached. The Applicant has included a warning in the SmPC Section 4.4 regarding a temporary reduction of vaccine protection lasting up to 4 weeks after treatment. This is agreed by CHMP.

No off-target biochemical interactions or physiological effects resulting from such interactions have been identified.

### *Additional expert consultations*

Experts in transplantation medicine were consulted by CHMP to provide input regarding the definition of the target population that would benefit most from treatment with imlifidase, and the study population, design and endpoints of the PAES proposed as obligation for a CMA. Minutes of the consultation are provided in Section 2.5.3 Discussion on clinical efficacy.

### *Additional safety data needed in the context of a conditional MA*

Safety experience with imlifidase is currently very limited and the uncontrolled nature of the studies limits the interpretability. However, given the lack of off-target effects of imlifidase and since it is proposed to be given only once (or potentially twice), the observed safety issues are considered manageable and long-term safety issues appear unlikely. Nevertheless, additional safety data are required to provide fully comprehensive data post-authorisation for a full marketing authorisation. Safety data will be gathered post-authorisation in particular as part of the specific obligations to the CMA and in a planned post authorisation efficacy study which was made condition to the Marketing Authorisation. This is agreed upon by CHMP.

## 2.6.2. Conclusions on the clinical safety

The safety experience with imlifidase is very limited and mainly based on the safety data analysed for 4 small completed clinical studies in patients with CKD. This is considered acceptable considering the rarity and severity of the disease, the high unmet medical need, and the fact that imlifidase is proposed for single use only which can be repeated, if needed, within 24 hours after the first dose. The described toxicities are considered manageable. The main safety concerns are infusion-related reactions and infections, these risks are classified as important identified risks in the RMP and appropriate information and precautionary statements on these events are included in the SmPC. However, additional data are required post-marketing to provide fully comprehensive safety data.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- An ongoing observational long-term follow-up study to evaluate long-term graft survival and clinical outcome after imlifidase (study 17-HMedIdeS-14).

- A post-authorisation efficacy study (PAES) to evaluate 1-year graft survival, kidney function and safety after imlifidase (including severe and serious infections) (study 20-HMedIdeS-19).

Additional safety information will be collected in the planned prospective 5-year-extension observational follow-up study (Study 20-HMedIdeS-20).

## *2.7. Risk Management Plan*

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Infections | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.3, 4.4 and 4.8.<br>PL section 2 and 4. | Routine pharmacovigilance activities.<br><br>Additional pharmacovigilance activities:<br><br>17-HMedIdeS-14: An ongoing observational long-term follow-up study to evaluate long-term graft survival and clinical outcome after imlifidase.<br>Final study report 31 December 2023.<br><br>20-HMedIdeS-19: A post-authorisation efficacy study (PAES) to evaluate 1-year graft survival, kidney function and safety after imlifidase (including severe and serious infections).<br>Final study report 31 December 2025<br><br>20-HMedIdeS-20: A 5-year-extension post-authorisation efficacy study (PAES) to evaluate long-term graft survival in patients who have undergone kidney transplantation after imlifidase administration.<br>Study synopsis November 2020.<br>Final study report 31 December 2030. |
| Infusion–related reactions | Routine risk communication:<br>SmPC section 4.2., 4.4 and 4.8.<br>PL section 2, 3 and 4. | Routine pharmacovigilance activities.<br><br>Additional pharmacovigilance activities:<br><br>17-HMedIdeS-14: An ongoing observational long-term follow-up study to evaluate long-term graft survival and clinical outcome after imlifidase.<br>Final study report 31 December 2023.<br><br>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).<br>Final study report 31 December 2025<br><br>20-HMedIdeS-20: A 5-year-extension post-authorisation efficacy study (PAES) to evaluate long-term graft survival in patients who have undergone kidney transplantation after imlifidase administration. |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | | Study synopsis November 2020.<br>Final study report 31 December 2030. |

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

## *2.8. Pharmacovigilance*

### *Pharmacovigilance system*

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD) because the product is not yet licensed in any country, hence the EBD will be the IBD. The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

## *2.9. New Active Substance*

The applicant declared that imlifidase has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers imlifidase to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

## *2.10. Product information*

### 2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.10.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

- The Group accepted an English-only outer carton and vial label.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed

materials will only be translated in the language as agreed by the QRD Group.

### 2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Idefirix (imlifidase) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product authorised after 1 January 2011;
- It is approved under a conditional marketing authorisation

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The indication applied for by the Applicant is desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased-donor.

Chronic renal failure, especially ESRD is a seriously debilitating and life-threatening condition. The health and survival benefits of renal transplantation of patients with ESRD compared with staying on dialysis are well established, in addition to the major improvements in QoL.

It is well established that the presence of DSA is a major barrier for successful transplantation of kidneys. Thus, highly sensitized patients usually cannot be transplanted within a reasonable timeframe but remain on dialysis with substantially shorter life expectancy and QoL.

The target population is highly sensitized patients awaiting kidney transplantation who, due to their broad anti-HLA antibody profile, are highly unlikely to receive a compatible kidney transplant. These patients have no compatible living donor. For some of the patients, desensitization using currently available methods is successful in decreasing antibody titers to a level where a negative cross match can be obtained with a living donor. However, for the most sensitized patients and due to the breadth and strength of the antibodies, there is a very low likelihood of successful desensitization using currently available desensitization protocols.

### 3.1.2. Available therapies and unmet medical need

There is no approved therapy for desensitization, but a number of approaches are used to make sensitized patients eligible for transplantation. All of these use techniques to remove antibodies, e.g. plasmapheresis or immunoadsorption, often combined with B-cell depleting agents (e.g. rituximab and/or bortezomib), immunomodulatory agents (e.g. intravenous immunoglobulin [IVIg]) or

complement blockers (e.g. eculizumab). These treatments require repeated dosing for several weeks to months prior to transplantation and are almost exclusively used for living-donor kidney transplantation since deceased-donor kidney transplantations must take place within hours of donor death. Therefore, faster and more effective methods are needed to rapidly remove antibodies against a potential donor. Such treatment would address the unmet medical need to convert a positive crossmatch into negative and thereby allow deceased-donor kidney transplantation in highly sensitized patients. There are no approved medicinal products for enabling renal transplantation in sensitized patients.

### 3.1.3. Main clinical studies

An open-label, multicentre, uncontrolled, Phase II study (**study 06**) in 19 patients is the main study in support of this MAA together with 3 small uncontrolled Phase II clinical studies (02, 03, 04), which determined the most suitable dosing regimen and support the efficacy of imlifidase.

**Study 06** evaluated the efficacy of imlifidase in desensitizing 18 patients with a positive crossmatch test to an available living or deceased donor. The study included patients on the kidney transplant waiting list who had previously undergone desensitization unsuccessfully or patients who would not be candidates for standard of care desensitization due to a very high HLA antibody load. The study assessed imlifidase efficacy and safety in converting a positive crossmatch to negative by removing DSAs. 18 transplantations (5 living-donor and 13 deceased-donor) were performed within the study. One patient received an inadequate dose due to an infusion-related reaction and therefore was not transplanted. The study duration was 6 months and secondary objectives included kidney function, graft survival, PK, PD and immunogenicity of imlifidase. The planned imlifidase dose was 0.25 mg/kg, given once or, in case of lack of crossmatch conversion, a second time, within 2 days of the first infusion.

**Study 04** was a single-centre study, initiated in parallel with Study 03. The study included 17 highly sensitized patients with CKD, who were all transplanted with kidneys from deceased donors. 14 of these patients had failed desensitization with IVIG + rituximab and/or plasmapheresis, as part of standard of care for sensitized patients at this centre prior to inclusion in the study. 14 of the 17 patients had positive FCXM test (T- or B-cells or both) prior to imlifidase treatment. The planned imlifidase dose was 0.24 mg/kg, given once.

**Studies 02** and **03** were small early phase 2 ascending dose studies primarily investigating safety, PK and PD. Nevertheless, some clinical efficacy data were included in the pooled efficacy analysis.

Transplantation was part of the protocol of **studies 03, 04** and **06** but not of **study 02**.

**Study 13** retrospectively analysed follow-up data on patients from studies 02 and 03

**Study 14** is an ongoing long-term study currently following patients from studies 02, 03, 04, and 06.

## *3.2. Favourable effects*

The primary endpoint of the main **study 06** was: *"the ability to create a negative CXM test within 24 hours after imlifidase dosing."* For each patient, the primary endpoint was met if at least one assay was positive at pre-dose and the last assay within 24 hours post-dose was negative.

Of the 19 patients in the FAS, 17 patients (89.5%) were converted from a positive to a negative CXM, while 2 patients (10.5% of the FAS;) were not converted. One of the latter patients only received 25% of the dose due to an infusion reaction and the other subject had a borderline cross reactivity remaining after treatment and was transplanted considering the totality of data.

A secondary endpoint was donor-specific antibody (DSA) levels over time. At baseline, none of the 18 patients had a DSA MFI values <2,000, whereas 14 out of 18 (78%) did so 24h after imlifidase treatment. Although a secondary endpoint, time to crossmatch conversion could not be calculated due to many missing crossmatch tests within the 24 hours after administration of imlifidase.

All 17 patients with crossmatch conversion and one additional patient with a borderline crossmatch test were transplanted, and 16 patients had a functioning graft at end of study. Four of these patients had an eGFR ≥ 60 mL/min/1.73 $m^2$, 11 had an eGFR 30-59 mL/min/1.73 $m^2$, and 1 patient had an eGFR <30 mL/min/1.73 $m^2$ at end of study.

**Pooled analysis of studies 02, 03, 04, and 06:**
Patient data on the 46 patients that were transplanted after imlifidase administration were pooled for further analyses.

Crossmatch conversion

39 out of 46 (85%) transplanted subjects had a positive crossmatch before imlifidase treatment. In Study 04, crossmatch conversion was not an endpoint, thus post-dose crossmatch analyses were not performed. Of the 25 subjects with both a positive pre-dose crossmatch and post-dose data, 24 subjects (96%) converted to a negative crossmatch with imlifidase treatment. The remaining subject had borderline positive crossmatch but was transplanted based on all available data that suggested that transplantation was possible.

Patient and graft survival

Six months after transplantation, all subjects were alive and 43/46 (93%) of the grafts were functioning.

Three subjects lost their grafts; one subject in Study 04 and two subjects in Study 06
One subject experienced a hyperacute AMR and lost the graft during transplant surgery. The rejection was considered to be IgM-mediated and thus the event is not suggestive of lack of efficacy of imlifidase.
The two other subjects from **Study 06** were diagnosed with delayed graft function. Neither of the subjects could be taken out of dialysis during the study. Both subjects were treated for AMR starting at day 9 and day 28, respectively. In both cases, complicating factors were present, which were considered to be major contributors to the graft loss. Severe hypotension in one subject) and a previous history of three failed kidney transplantations due to severe AMR and thrombotic microangiopathy in the second subject were considered more probable explanations for graft loss in these cases than lack of efficacy of imlifidase. However, the observed rejection episodes may have contributed to the outcome.

Kidney function

42 subjects had a functioning kidney and eGFR data collected at the end of study. 38 of these 42 subjects (90%) had an eGFR ≥30 mL/min/1.73 $m^2$, corresponding to 83% of all transplanted subjects.

Antibody-mediated rejections (AMR)

15/46 (33%) subjects had at least one episode of antibody-mediated changes including the hyperacute rejection in one subject, described above.
11/46 subjects (24%) experienced biopsy-proven AMR combined with clinical signs, defined as active and/or chronic AMR, while 3 events (6.5%) were identified on analysis of a biopsy without any clinical signs and defined as subclinical, thus would not have been detected without protocol biopsies.

There was a higher proportion of AMR in EU-patients compared to US patients (40% vs 16%), but no firm conclusions could be drawn due to the limited number of subjects in the subpopulation analyses.

No AMR was seen in subjects without positive crossmatch, indicating a greater risk of AMR with positive crossmatch.

Long-term results

29 of the 46 patients transplanted in the feeder studies have been enrolled in the follow-up **Study 14**. Data from another 6 patients (3 with graft loss in the feeder studies and 3 who died after the feeder studies but before **Study 14** was started) were available. Eleven subjects eligible for inclusion in the study (i.e. having received a renal transplant in Study 02, 03, 04 or 06) were not enrolled. For two of these subjects, limited information was available. Six subjects lost their grafts or died before the start of **Study 14**.

Subgroup analysis in patients "highly unlikely to be transplanted without imlifidase treatment" (HUT):

Follow-up data (cut-off 30 September 2019) on **Study 14** were provided for the subgroups HUT v.s non-HUT. Information on 2 subjects are also included despite not being enrolled in the study. One of these subjects in the target population (HUT) was known to be alive with a functioning graft 2 years after transplantation, and the other subject in the complement population (non-HUT) was known to be alive with a functioning graft 1 year after transplantation.

Three graft losses occurred in the feeder studies (1 in the HUT population and 2 in the non-HUT population). Three graft losses were recorded more than 31 months after transplantation but before start of Study 14, 2 in the target (HUT) population and 1 in the complement (non-HUT) population. 2 of the 3 graft losses were due to lowering or non-compliance of immunosuppression medication, and the third was the eventual outcome of a prolonged delayed graft function (**Table 46**).

Three deaths have been reported, all in the target population, all occurring in the period 7-12 months after transplantation (**Table 47**). None of the deaths is regarded as having any relationship to kidney malfunction. Kidney function assessments show that the majority of the patients have a satisfactory or well-functioning kidney.

Kidney function assessments show that the majority of the patients have a functioning kidney (**Table 48**).

Adjudication of the rejection episodes based on the Banff 2017 criteria reported in **Study 14** show that 1 of the proposed episodes, occurring in the period 6 months to 1 year after transplantation, fulfilled all the criteria to be classified as an AMR (**Table 49**). The event was reported in a HUT patient.

In summary, 85% (17/20) of the subjects with data available from 3-year FU were reported with a functioning graft. Due to a large number of missing observations, no firm conclusions on 3-year graft survival can be drawn.

## *3.3. Uncertainties and limitations about favourable effects*

A substantial change in manufacturing has been introduced to drug substance and drug product, leading to differences in pharmacological activity, in formulation and impurity profile between material produced under process 1 (before change) and process 2 (after change). Only material from process 1 has been used in clinical studies and in most of the non-clinical studies, but material manufactured by process 2 is the intended commercial product. For bridging from process 1 to process 2 material, the Applicant has provided, in response to CHMP request, a comprehensive analytical comparison, *in vitro* PD data and results of a PK/PD study in 20 healthy subjects using process 2 material (**study 15**). These data show that process 2 material is purer and 2-times more potent than process 1 material but, more importantly, IgG degradation *in vitro* (using human plasma) and *in vivo* is largely comparable, probably owing to the presence of pre-existing ADAs. Because of these findings and due to the fact

that imlifidase is highly specific for degrading IgG and no off-target effects have been identified or can be expected, it is concluded that the clinical performance of the products from the two different processes to be similar.

Six subjects were excluded in **study 15** because of the exclusion criterion: anti-imlifidase IgG >22 mg/L. This exclusion criterion was considered problematic by CHMP, since patients will not be tested for their anti-imlifidase levels prior to administration of imlifidase.

In earlier clinical studies, patients with pre-dose anti-imlifidase levels of over 30 mg/L were included. The applicant provided the information that only two subjects had pre-dose anti-imlifidase antibodies > 22 mg/L, and in both a single dose of 0.25 mg/kg imlifidase process 1 material resulted in a negative cross-match test. While the exclusion of subjects with pre-dose anti-imlifidase IgG >22 mg/L in **study 15** is unfortunate, the totality of data suggests that data from process 1 material in subjects with pre-dose anti-imlifidase IgG >22 mg/L can be extrapolated to process 2 material. Process 2 material is expected to be at least as efficacious as process 1 material, irrespective of the level of pre-dose anti-imlifidase IgG.

Pre-dose DSA with mean fluorescens intensity (MFI) >2,000, which is considered a contraindication to transplantation in many transplant centres, was reported for 43/46 (93%) transplanted subjects. 38 of these 43 subjects (88%) had no DSA with an MFI value > 2,000 at 24 hours after administration.

Although the medical need for an effective desensitization treatment to make highly sensitized CKD patients eligible for kidney transplantation is undisputed by CHMP, it was unclear to CHMP whether the study population was sufficiently representative of the target population and whether the efficacy results obtained would be over-estimated. The Applicant provided further details and discussion on the sensitisation status of the study subjects and analyses in a subgroup most closely resembling the target population. The 3 criteria used to define the "highly unlikely to be transplanted (HUT) without prior imlifidase treatment" patients are: 1) cPRA of ≥95% based on a mean fluorescence intensity (MFI) cut-off of 3000, or a historical peak PRA of ≥95%, 2) Deceased donor (DD) transplantation, and 3) Positive XM (determined by CDC or flow cytometry XM test) towards the available graft immediately prior to imlifidase treatment and transplantation. AMR incidence was increased about 2-fold in the HUT (N=25) versus the complementary non-HUT (N=21) subgroup but without obvious effects on graft survival or graft function, suggesting that AMR episodes were successfully treated. However, AMR has been implicated in reduced long-term graft survival. Additional and longer-term data will be needed to further address this uncertainty in the context of the conditional marketing authorisation.

In **Study 06**, 7 different crossmatch tests could be used. The Applicant was asked to clarify the relevance of the different crossmatch tests with regard to transplantability and resulting benefit of crossmatch conversion. For example, Eurotransplant considers only a positive CDC test as clear contraindication for transplantation/organ allocation. The Applicant summarised the information on the different types of crossmatch tests used in clinical practice: cell-based flow cytometry (FCXM), cell-based complement-dependent cytotoxicity (CDCXM) and virtual crossmatch (vXM) based on single antigen bead analysis. vXM is a theoretical method providing only a preliminary result that needs to be confirmed by FCXM or CDCXM, and therefore could not be used stand alone. According to applicant, the clinical practice at most transplantation centres is FCXM using T- and B-cells from the donor. This method is more sensitive than CDCXM but is also associated with a high risk of false positive results. However, both methods are being used at the certified laboratories of different transplant centres for determining crossmatch status. Some regions, national authorities, and allocation systems specify which test is to be used (e.g. CDCXM in the Eurotransplant network), whereas in other countries, the certified laboratory can decide which XM test to be used. The applicant stated that therefore it is not possible to recommend a specific crossmatch test. This is agreed upon by CHMP that the use of imlifidase should not be tied to the use of a specific CXM.

However, the ad-hoc expert group (AHEG) cautioned about transplantation in T-cell CDCXM test positive ESRD patients since the outcome of transplantations in such patients have so far been poor. Patients with positive CDCXM tests are those with the highest level of sensitisation and the highest risk of AMR and graft loss. Regarding the proposed target population, the expert group considered that the available data are not sufficient to support the use of imlifidase in the treatment of patients with positive T-cell CDCXM test. Only 3 patients had a positive T-cell CDCXM test against the actual donor reported before imlifidase administration. Two of these subjects had a post-treatment CDCXM test (both negative). All three patients could be transplanted with the help of imlifidase and none of these patients lost their graft during follow-up. There is no mechanistic rationale for why imlifidase would work less efficiently in positive T-cell CDCXM than in other situations as it is the same antibodies that should be cleaved. It can be concluded that there is very limited experience in patients with a confirmed positive T-cell CDCXM before imlifidase treatment, but this should not preclude use of imlifidase in this setting. Information on the very limited experience in patients with positive T-cell CDCXM test is reflected in Section 4.4 of the SmPC. Additional data in these subgroup population will be collected post marketing, since T-cell based CDCXM testing against the donor should be performed whenever possible in the planned 1-year post-authorisation efficacy study.

Study subjects could receive a second dose of imlifidase in case no crossmatch conversion was observed after the first dose but the initially proposed posology did only foresee a single dose. Since an effect of ADAs on the PD of imlifidase within the first 24 hours after first imlifidase is considered negligible, the applicant agreed to amend Section 4.2 of the SmPC upon CHMP request, to include the possibility of an additional dose of 0.25 mg/kg within 24 hours if the first dose is found to be insufficient to achieve crossmatch conversion.

The database is very limited, especially with regard to long-term data on graft survival and function. Although the available outcome data are considered encouraging, additional data are required to be provided post-marketing to confirm the longer-term results on graft survival and function in the context of the conditional marketing authorisation (CMA). In this context, the rate of AMR is of concern as episodes of AMR are considered a risk factor for shorter graft survival.

Imlifidase antibodies are very common in the target population. However, neutralizing ADA, especially high levels, may affect the efficacy of imlifidase. The influence of ADA in case of a second (or more) time use of imlifidase in a re-transplantation setting is currently not known and a negative influence of ADA on the efficacy of imlifidase in that case cannot be ruled out. This is acceptable since Imlifidase is for one-time use only (one or two doses within 24 hours).

The applicant applied for a CMA. Two specific obligations, the completion of the ongoing extension study 14 and the conduct and submission of results of a 1-year PAES to further investigate graft survival and graft function in ESDR patients transplanted with the help of imlifidase, have been proposed by the applicant.

The PAES is a non-randomised study in 50 highly sensitized ESRD patients with comparison to a historical control group and a concurrent non-imlifidase treated control group (1-2 controls per subject up to a maximum of 100 patients) recruited from the same study sites. The Applicant was asked to discuss and justify the design of the proposed PAES. The Applicant provided a comprehensive discussion on the possibility to perform either an RCT similar to the US study planned together with the FDA or an RCT comparing imlifidase to other sensitisation methods. As summarised by the applicant, there are no harmonised approaches for deceased-donor organ allocation across the EU, with each country, region or network defining their own organ allocation policy. As a consequence, the possibility of receiving a suitable organ at a given level of sensitisation varies in the EU. Furthermore, the nation-wide US Kidney allocation system with its large population has an advantage over the smaller regional and national priority programmes in the EU in finding a matching kidney also for highly sensitised

subjects. In a RCT similar to the US study, comparing long term outcome in subjects transplanted after imlifidase treatment to subjects remaining on the waiting list for a suitable kidney, a lower probability of subjects in the control arm receiving a transplant together with a considerable heterogeneity in standard of care between the study sites would hamper the interpretability of the results. Furthermore, no desensitisation protocols are currently approved as safe and effective within the EU in a deceased donor setting. The non-randomised study design is therefore agreed by CHMP. The applicant agreed to the study amendments proposed by CHMP such as the inclusion of site-matched subjects to address differences in experience and clinical practice across sites in the concurrent control group and performance of protocol biopsies of the transplanted grafts to investigate the occurrence of AMR. Protocol will be submitted in December 2020 for agreement by CHMP and final report is due in December 2025.

A 5-year extension study to the 1-year PAES will be conducted to evaluate longer-term graft survival in patients who have undergone kidney transplantation after imlifidase. This study is a condition for the marketing authorisation and is necessary under Article 9(4)(cc) of Regulation 726/2004 and Article 1(1)(a) and 1(2)(d) of Regulation 357/2014 to address concerns with a potential lack of efficacy in the long term with respect to the maintenance of a positive benefit-risk balance, and which can only be resolved after the product has been authorised.. The study synopsis is planned to be submitted in November 2020 for agreement by CHMP and final results due in December 2030.

The Applicant commits to submit the results of the planned FDA study to EMA when available.

## *3.4. Unfavourable effects*

Due to its mechanism of action that leads to profound hypogammaglobulinaemia, imlifidase is expected to substantially increase the risk of bacterial infections. Severe and serious infection, infusion-related reaction, myalgia and transplant rejection were determined as AESIs.

Nine of the 54 subjects (17%) exposed to imlifidase had at least 1 related AE within the potential AESI of 'Severe or serious infections'. Related AEs (PTs) within this potential AESI that occurred in > 1 subject included pneumonia (3 patients) and sepsis (2 patients). It is agreed by CHMP that transplantation itself and maintenance immunosuppression may have contributed to this type of events. Adequate information on infection and infection prophylaxis is given in 4.4 of the SmPC

Five subjects had at least 1 related AE within the potential AESI 'Infusion-related reactions', including 3 of 54 patients with CKD. One of the 3 related infusion-related reactions in patients with CKD was serious and resulted in treatment and study discontinuation. The proposed SmPC texts are addressing this inherent risk. Premedication using corticosteroids and antihistamines is endorsed by CHMP. The SmPC provides a recommendation as to when the infusion should be discontinued and when the infusion could be restarted following an infusion-related reaction.

One of the 54 patients (2%) with CKD experienced 'severe or serious myalgia' 2 days after the second dose of 0.25 mg/kg imlifidase, which did not resolve during the study and was assessed as related to imlifidase.

11 of the 46 transplanted patients (24%) had a biopsy-proven or presumed AMR. A total of 15 of 46 patients (33%) had any antibody-mediated change. One transplant rejection (SAE) was assessed as related to imlifidase. Myalgia is described in 4.8 of the SmPC.

Precautionary statements on Antibody-mediated rejection are provided in 4.4 of the SmPC.

Imlifidase is a cysteine protease that specifically cleaves IgG. As a consequence, IgG-based medicinal products may be inactivated if given in connection with imlifidase. Antibody-based medicinal products

cleaved by imlifidase include, but are not limited to basiliximab, rituximab, alemtuzumab, adalimumab, denosumab, belatacept, etanercept, rabbit anti-thymocyte globulin (rATG) and intravenous immunoglobulin (IVIg). This is stated as a precautionary statement in 4.4 of the SmPC and section 4.5 recommends time intervals between administration of imlifidase and antibody-based medicinal products).

Due to the reduced IgG levels after treatment with imlifidase, there is a risk for a temporary reduction of vaccine protection for up to 4 weeks following imlifidase treatment. This is appropriately described in the SmPC.

## *3.5. Uncertainties and limitations about unfavourable effects*

The safety evaluation is based on clinical data obtained with process 1 material. Process 2 drug product, which is the intended commercial product, has only been used in **study 15,** a study in healthy men, randomising 20 healthy men aged 18 to 55 years to imlifidase (n=15) or placebo (n=5). The safety profile seems comparable with safety data of process 1 material. Although, the safety of the commercial product has not been studied in patients with CKD, the higher potency of the purer process 2 material is unlikely to lead to safety issues since imlifidase highly specifically cleaves IgG without known off-target effects. Therefore, it is acceptable to generate patient data with process 2 material in post-marketing studies.

The small database, the uncontrolled nature of the data and the heterogeneous study population and concomitant medications limit robust evaluation of the imlifidase safety profile. The applicant proposes the final study report of Study 14 and a PAES to be conducted as post-marketing activities to provide comprehensive data and to investigate long-term efficacy and safety. A separate extension study to the 1-year PAES will also be conducted to collect data up to five years.

Patients received different doses and a different number of doses. As the study population is very small, it is not entirely clear whether different doses might have an impact on the safety profile. There was no apparent dose-related difference in the post-treatment level of ADA between 2 doses. There were no indications that infusion-related reactions were dose-dependent. Across dosing regimens, the pattern of AEs was similar to that of kidney-transplanted patients not receiving imlifidase.

After imlifidase administration, the IgG levels start to increase again after 1-2 weeks but may be suppressed up to approximately 1 month after treatment with imlifidase or until IVIg is administered (most patients received IVIg 1-2 weeks after transplantation). To mitigate the risk of infections, prophylactic antibiotics were used until IVIg was administered or IgG levels returned to acceptable values. Cases of infection occurred despite prophylaxis, but this is also the case in the general transplantation setting. Compared with the standard of care after kidney transplantation in general, an oral antibiotic agent covering bacteria causing respiratory tract infections was added to reduce the potentially increased risk of such infections, as these are the most common in patients with hypogammaglobulinemia. Overall, the pattern of infections observed in transplanted patients after imlifidase treatment is consistent with the pattern of infections reported in patients not treated with imlifidase. In line with the study conditions, the SmPC recommends the use of prophylactic oral antibiotics covering respiratory tract pathogens for 4 weeks in addition to the standard of care infection prophylaxis in kidney transplantation in general (against *Pneumocystis carinii*, cytomegalovirus and oral *candida*).

Elevated liver enzymes were observed in patients at least once after imlifidase administration; however, no subjects fulfilled the criteria for Hy's law. There are no clear indications that imlifidase is hepatotoxic or contributes to elevated liver enzymes in kidney-transplanted patients. There is currently

no mechanistic rationale for hepatotoxicity. The role of imlifidase in the occurrence of elevated liver enzymes remains unclear and no firm conclusions can be drawn from the presented data.

As the studies were single-arm uncontrolled studies in a heterogenous and small population, not all issues could be completely elaborated. Additional safety data will be generated post-marketing from the completion of the ongoing Study 14 and in the planned post authorisation efficacy study which are specific obligations to the CMA, and from the 5-year extension of post authorisation efficacy study which is an Annex II condition.

## *3.6. Effects Table*

**Table 62 Effects Table for imlifidase (cut-off date 30Sep2019)**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects (study 06)** | | | | | | |
| Crossmatch conversion | The ability to create a negative CXM test within 24 hours after imlifidase dosing | No (%) of patients | 17 patients (89.5%) were converted from a positive to a negative CXM | NA | CMX may refer to one of overall 7 concrete cross-matches (CMXs) performed - namely FACS T, FACS B, amplified CDC T, amplified CDC B, not-amplified CDC T, not-amplified CDC B, and virtual CXM - at currently unclear time points, unclear frequencies, and partially unclear (deceased, living, virtual) donors available for each of the 7 CXMs. | See "clinical efficacy section |
| **Favourable Effects (across the studies)** | | | | | | |
| Crossmatch conversion | The ability to create a negative CXM test within 24 hours after imlifidase dosing | No (%) of patients | 24 subjects (96%) converted to a negative crossmatch. | N/A | 39/46 (85%) transplanted subjects had a positive crossmatch before imlifidase treatment. In Study 04, crossmatch conversion was not an endpoint, thus post-dose crossmatch analyses were not performed. Of the 25 subjects with both a positive pre-dose crossmatch and post-dose data, 24 subjects (96%) converted to a negative crossmatch with treatment | |

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Elimination of donor specific HLA antibodies (DSAs) | The ability to eliminate DSAs (measured as MFI <2,000) at 24 hours after imlifidase administration | No (%) of patients | 43 subjects (88%) had no DSA with an MFI value > 2,000 | N/A | | |
| Graft survival | Graft survival at 6 months after the transplantation | No (%) of patients | 43(93%) | N/A | Three subjects lost their grafts; one subject in Study 04 and two subjects in Study 06. | |
| Kidney function | Functioning kidney at 6 months after the transplantation (eGFR ≥ 30 mL/min/1.73 $m^2$ | No (%) of patients | 38(83%) | N/A | Renal function was stratified in three groups; <30, 30-59 and >60 mL/min/1.73 m2. Due to the limited number of transplanted subjects, the number of subjects in each subpopulation is inevitable small. | |
| **Unfavourable Effects** | | | | | | |
| Severe and serious infections | Mainly pneumonia and sepsis | % of patients | 40.7% (22/54)<br><br>16.7% (9/54) were considered related | NA | Relationship to treatment plausible<br><br>Lack of control in a very heterogeneous population | See "clinical safety section" |
| Infusion related reactions | PTs reported: Infusion related reaction, Flushing, Dyspnoea | % of patients | 7.4% (4/54)<br><br>5.6% (3/54) were considered related | NA | | |
| Myalgia | | % of patients | 1.9% (1/54) (related) | NA | | |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The high medical need for an effective desensitizing agent to improve transplantability of patients on dialysis that are highly sensitized against donor kidneys is acknowledged by CHMP. Imlifidase was shown to quickly and effectively degrade IgG antibodies, thereby leading to crossmatch conversion

with subsequent kidney transplantation in a high percentage of sensitized CKD patients. However, in most cases conversion was shown for FCXM tests. Only 3 patients had a positive T-cell CDCXM tests against the actual donor reported before imlifidase administration and two of them seem not to have a post-treatment CDCXM test (both negative after imlifidase). However, all 3 patients could be successfully transplanted with the help of imlifidase.

The Applicant has revised the initially proposed therapeutic indication to clarify that imlifidase should be used complementary to and not instead of the existing allocation programmes for subjects anticipated to have a very low chance of finding a matching kidney despite the efforts within such programmes. This is appropriately reflected in section 4.1 of the SmPC: *"The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritization programmes for highly sensitized patients".*

All subjects for whom a donor kidney became available and who received the planned imlifidase dose(s) were successfully transplanted, including the 25 HUT subjects as defined by the Applicant, which is the subpopulation most representative of the target population.

The benefit of Idefirix is considered important by CHMP since Idefirix has successfully allowed highly sensitised patients to receive a kidney transplant.

Three subjects could never be taken out of dialysis after transplantation, but the remaining subjects had functioning renal grafts at the end of the study (6 months after transplantation) with 90% of the 42 subjects with a functioning kidney and eGFR data collected at the end of study having an eGFR ≥30 and 36% ≥60 mL/min/1.73 m2, indicating benefit of imlifidase up to six months. This includes the 3 patients with positive T-cell CDCXM test pre-dose. Two of these patients experienced an AMR but at about 2 years after transplantation, all 3 had maintained their grafts. Based on the available data, there is no rationale for a different effect in positive T-cell CDCXM.

Nevertheless, the AHEG cautioned about transplantation in T-cell CDCXM test positive ESDR patients since the outcome of transplantations in such patients have so far been poor. In a general renal transplant population, a 5-year graft survival around 95% is typically reported. It is acknowledged by CHMP that a comparison to the general population is not completely adequate, as the imlifidase population have several risk factors for shorter graft survival, mainly positive crossmatch and a high occurrence of DSA, but also a lower percentage of living donors and, in many cases, a longer time on dialysis. However, given the lack of renal donors, the graft survival time after transplantation is of importance for the benefit/risk of imlifidase. The SmPC contains adequate information in Section 4.4 that the experience with the use of imlifidase in patients with positive T-cell CDCXM test is very limited. Additional data will be collected post marketing in patients with positive T-cell CDCXM, since T-cell based CDCXM testing against the donor should be performed whenever possible in the planned post-authorisation efficacy study.

Currently, the long-term data on imlifidase is scarce and follow-up data beyond 6 months is missing in 11 out of 46 transplanted patients. This is considered by CHMP one of the major uncertainties regarding the benefit of imlifidase. Although the short-term and very limited longer-term outcomes support a CMA, further information on long-term renal function and graft survival is considered necessary for a full approval. In this context, the rate of AMR is of concern. The rejection rate reported in the imlifidase development programme and especially in the highly sensitized HUT subpopulation is higher than reported in e.g. the article by Shaffer et al, describing a similar population. Even though the AMR described were successfully treated in imlifidase studies, it is known from the literature (Lefaucheur 2010) that episodes of AMR is a risk factor for shorter graft survival.

The Applicant proposed a PAES as special obligation for a CMA to provide additional short (1 year) term data and to confirm efficacy and safety of imlifidase in the indication applied for. Although the ad-

hoc expert group considered a randomized controlled trial in highly sensitized patients feasible and a historical control group unsuitable, the Applicant stated that a RCT would not be feasible in the target population due to the situation in the EU without a common kidney allocation system, different local Acceptable Mismatch (AM) programmes and the fact that no desensitisation protocols are currently approved as safe and effective within the EU in a deceased-donor setting. The CHMP followed the argumentation of the Applicant and considers the study design acceptable and the proposed study outcomes important and meaningful. A separate extension study to the 1-year PAES will be carried out to collect 5-year follow-up data to address the uncertainties on long-term efficacy.

Based on the mechanism of action of imlifidase, the AEs of severe and serious infections, infusion-related reactions, myalgia and transplant rejection were determined as adverse events of special interest (AESIs). Overall, the unfavourable effects are considered to be manageable, especially considering that transplant centers are well equipped and experienced in dealing with such issues.

As the safety evaluation of imlifidase was hampered due to the lack of a control arm, the small and heterogeneous study population, and the use of various other medications in this severely ill patient population, there remains some uncertainty regarding the contribution of imlifidase treatment of the observed AEs. However, it should be noted that the effect of imlifidase is short and therefore long-term safety issues are not expected. Additional safety information will be collected as part as the specific obligations to the CMA (completion of **study 14** and planned PAES).

## 3.7.2. Balance of benefits and risks

The short-term benefit of Idefirix is considered adequately shown for patients with a positive XM test and unlikely to receive a matching kidney graft from a deceased donor. The Applicant clarified that imlifidase should be used complementary to and not instead of the existing allocation programmes for subjects anticipated to have a very low chance of finding a matching kidney despite the efforts within such programmes. This has been made clear by the revised wording in section 4.1 of the SmPC.

Although, experience with imlifidase is very limited in patients with the highest degree of sensitisation, i.e. those with a positive T-cell CDCXM test, such patients should not be excluded from treatment with imlifidase based on the information available. Information on the very limited experience in patients with positive T-cell CDCXM test is reflected in Section 4.4 of the SmPC. Additional data will be collected post marketing in such patients, since T-cell based CDCXM testing against the donor should be performed whenever possible in the planned 1-year post-authorisation efficacy study.

Overall, imlifidase is considered to address an unmet medical need by providing a rapid desensitisation technique for enabling kidney transplantation in highly sensitised adult subjects with donor specific antibodies and a positive crossmatch to a potential deceased donor. Especially, patients with extended waiting periods in a mismatch programme or on other waiting lists and considered of having very low chances of receiving a matching donor organ may benefit from imlifidase.

The safety profile appears acceptable for one-time (one or two doses) use although this is only based on uncontrolled data and a small number of patients. The safety profile of imlifidase treatment (e.g. hypersensitivity reactions, infections) is not benign but considered manageable.

The Applicant has applied for a CMA with an acceptable proposal to generate comprehensive data post-marketing.

## 3.7.3. Additional considerations on the benefit-risk balance

### *Conditional marketing authorisation*

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004, as it aims at treating a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance of Idefirix is positive in the target population of highly sensitized patients waiting for kidney transplantation, who, due to their broad anti-HLA antibody profile, are highly unlikely to receive a compatible kidney transplant, as discussed in Section 3.7.2. The available data demonstrates a clear benefit, because Idefirix allowed all patients to receive a renal transplant. It is acknowledged by CHMP that long-term efficacy data is scarce and more information on safety is required. However, the demonstrated risk to patients is manageable. Therefore, the benefits of enabling highly sensitised patients to receive a kidney transplantation outweigh the risk inherent to the lack of comprehensive information.
- It is likely that the applicant will be able to provide comprehensive data.

  The evidence provided is based on small exploratory trials. Submitted data are therefore considered non-comprehensive. Additional and longer-term efficacy data and additional safety data are required to provide comprehensive data. Two post-authorisation measures (ongoing extension **Study 14** and a planned post authorisation efficacy study) will be conducted as special obligations.

  **- Study 14** (ongoing) is an observational long-term follow-up to evaluate the long-term graft survival in patients who have undergone kidney transplantation after imlifidase administration. The study is ongoing and the required data are expected to be provided in December 2023.

  - **Post authorisation efficacy and safety (PAES) study** (planned) will further evaluate efficacy and safety of imlifidase in 50 highly sensitized ESDR subjects with a positive crossmatch, having been transplanted after pre-treatment with imlifidase. The study will include two non-comparative reference cohorts for descriptive purpose; one registry-based historical reference cohort with kidney-transplanted patients and a second concurrent reference cohort with transplanted patients (any grade of sensitization). T-cell based CDCXM testing against the donor should be performed whenever possible.

  Efficacy endpoints will be 1-year graft survival rate, percentage of patients alive at 1 year with a functioning graft, kidney function and patient survival, frequency of crossmatch conversion, in addition to safety profile (including serious and severe infections, and infusion-related reactions) and QoL. The study protocol is planned to be submitted in December 2020 and the study report in December 2025.

  Both studies will evaluate additional long-term effectiveness and safety and are considered to be feasible within the proposed timeframe.
- Unmet medical needs will be addressed, as
  - Renal transplantation remains the optimal treatment for patients with CKD compared to continued dialysis. It is well established that the presence of DSA is a major barrier for

successful transplantation of kidneys. Thus, these patients usually remain on dialysis with shorter life expectancy and impaired QoL. Renal failure is therefore a seriously debilitating and life-threatening disease.

  - There are no medicinal products explicitly approved for enabling renal transplantation from deceased donors in highly sensitized patients. For living donor transplantations, desensitization methods are available for successful transplantation. However, in the case of deceased donor kidneys, these methods are usually not feasible due to the very limited time available. Most desensitisation treatments require repeated dosing prior to transplantation and are almost exclusively used for living-donor kidney transplantation since deceased-donor kidney transplantations must take place within hours of donor death. There are no developments in the area of the therapeutic indication other than further development of extracorporeal methods and equipment such as plasmapheresis and immunoadsorption, which are infrequently used in the case of deceased donor transplantations.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  - Idefirix has been shown to convert positive crossmatch into negative crossmatch and to allow renal transplantation in highly sensitized patients unlikely to receive a matching kidney graft from a deceased donor. In view of the encouraging short-term and very limited longer-term efficacy results available with Idefirix, there is a clear benefit of immediate availability for all patients in the target population.

  - The safety profile of Idefirix is manageable. Limitations result from the fact that the number of patients investigated is low, for reasons linked to the rare setting of the treated condition.

  - Long-term efficacy information on graft functioning and survival is still required to confirm the benefits of Idefirix to allow successful renal transplantation in the target population.

  Considering the unmet medical need and the encouraging outcomes of highly sensitized ESDR patients having received a deceased donor kidney transplant after pre-treatment with imlifidase, benefits to public health of the immediate availability of Idefirix outweigh the uncertainties inherent to the current limitations of longer term and more comprehensive efficacy and safety data. Delaying the approval of Idefirix would thus be disproportionate from the public health perspective.

## *3.8. Conclusions*

The overall B/R of Idefirix is positive in the following therapeutic indication:

*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.*

# 4. Recommendations

## *Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Idefirix is favourable in the following indication:

*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.*

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

## *Conditions or restrictions regarding supply and use*

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## *Other conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|---|---|
| Postauthorisation efficacy study (PAES): to further investigate the long-term graft survival in patients who have undergone kidney transplantation after Idefirix administration. The MAH should conduct and submit the results of a prospective 5-year-extension observational follow-up study. | December 2030 |

## *Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation*

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

| Description | Due date |
|---|---|
| To confirm the long-term efficacy of Idefirix in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor, the MAH should submit the results of a prospective, observational long-term follow-up study to evaluate long-term graft survival in patients treated with imlifidase prior to kidney transplantation. | December 2023 |
| To confirm the long-term efficacy and safety of Idefirix in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor, the MAH should conduct and submit the results of a controlled, open-label post-approval study investigating 1-year graft survival rate in kidney transplant patients with positive crossmatch against a deceased donor after desensitisation with imlifidase. | December 2025 |

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States*

Not applicable.

## *New Active Substance Status*

Based on the CHMP review of the available data, the CHMP considers that imlifidase is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.