EU Risk Management Plan (RMP) for Idefirix (imlifidase)

RMP version to be assessed as part of this application:

RMP version number:	2.0
Data Lock Point for this RMP:	25-Aug-2023
Date of final sign off:	22-May-2024

Rationale for submitting an updated RMP:	The updated RMP is considered to be significant as the specific obligation of study 17-HMedIdeS-14 (Category 2) has been completed and fulfilled
Summary of significant changes in this RMP:	• Part II: Module SIII - Clinical trial exposure updated with final data / 5-year outcome from study 17-HMedIdes-14 • Part IV: Plans for post-authorisation efficacy studies updated with study status (study 17-HMedIdeS-14 removed as study has been completed and obligation has been fulfilled) • Part V: Summary of risk minimisation measures updated with status of the additional pharmacovigilance activities per safety concern (study 17-HMedIdeS-14 removed as study has been completed and obligation has been fulfilled) • Annex 5 – Protocols for proposed and on-going studies in RMP part IV updated with study status (study 17-HMedIdeS-14 removed as study has been completed and obligation has been fulfilled)
Other RMP versions under evaluation:	Not applicable
Details of the currently approved RMP:	Version number: 2.0 Approved with procedure: EMEA/H/C/004849/II/0019 Date of approval (opinion date): 16-May-2024

QPPV name:	Mette Kallesøe
QPPV signature:	The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Imlifidase
Pharmacotherapeutic group(s) (ATC Code)	L04AA41 (Selective immunosuppressant)
Marketing Authorisation Applicant	Hansa Biopharma AB
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Idefirix
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Protease
	Summary of mode of action The mode of action of imlifidase is by cleaving human immunoglobulin G (IgG).
	Important information about its composition: The active substance, imlifidase, is a cysteine protease derived from an IgG-degrading enzyme of *Streptococcus pyogenes*, and produced in *Escherichia coli* cells by recombinant deoxyribonucleic acid (DNA) technology.
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Current: Idefirix is indicated for desensitisation treatment of highly sensitized adult kidney transplant patients with a 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 prioritization programmes for highly sensitized patients.
	Proposed (if applicable): Not applicable (NA)
Dosage in the EEA	Current: Treatment should be prescribed and supervised by a specialist physician experienced in the management of immunosuppressive

	therapy and sensitized renal transplant patients. Idefirix should be restricted to hospital use only. The dose is based on patient body weight (kg). The recommended dose is 0.25 mg/kg administered as a single dose intravenously, preferably within 24 hours prior to transplantation. One dose is adequate for crossmatch conversion in the majority of patients but if needed a second dose can be administered within 24 hours after the first dose. For instructions on reconstitution and dilution of the medicinal product before administration, see SmPC section 6.6.
	Proposed (if applicable): Not applicable (NA)
Pharmaceutical form(s) and strengths	Current (if applicable): Powder for concentrate for solution for infusion, 11 mg
	Proposed (if applicable): Not applicable (NA)
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication: Idefirix is indicated for desensitization treatment of highly sensitized 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 prioritization programmes for highly sensitized patients.

Background for calculation of incidence and prevalence

Approximately one third of patients waiting for kidney transplantation are sensitized to potential donor tissues, i.e. they have antibodies against human leukocyte antigens (HLAs) (Iyer et al. 2013). The presence of donor-specific anti-HLA antibodies (DSAs) and a positive crossmatch are considered a contraindication to transplantation since DSAs may cause immediate damage to the graft. In worst case, this leads to hyperacute rejection or early antibody-mediated rejection (AMR) resulting in graft failure and return to dialysis (Montgomery et al. 2004; Terasaki et al. 2005).

As publications on the incidence and prevalence of highly sensitized patients in Europe, who would be eligible for kidney transplantation if they were not highly sensitized are scarce, the following data were taken into account for incidence and prevalence calculations:

- Based on data published by Eurotransplant, 5.2% of the patients active on the kidney transplantation waiting-list at the end of 2018 had panel-reactive antibodies (PRA) of 85-100% (Eurotransplant 2019).
- 13%-15% of the patients on the transplantation waiting-list have been reported to be highly sensitized, defined as having calculated panel-reactive antibodies (cPRA) of at least 80% (Hart et al. 2018; Iyer et al. 2013).
- In the UK, 26% of patients on the waiting-lists have been reported to be highly sensitized with a calculated reaction frequency (cRF) of at least 85% (Manook et al. 2017).

Based on these data, ranging from 5.2% to 26% of patients being highly sensitized, it was considered acceptable to assume that 15% of the patients active on the kidney transplantation waiting-list are highly sensitized; this percentage will be used below with reference to the publication by Iyer et al. (Iyer et al. 2013).

Incidence

The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) has published registry data from 34 European countries covering a general population of 677 million inhabitants, representing 80.5% of the 2016 European general population. Based on ERA-EDTA registry data, 83,311 individuals commenced treatment for end-stage renal disease (ESRD) in 2016 (Kramer et al. 2019) . If excluding the 4% who received a pre-emptive kidney transplant, this corresponds to approximately 80,000 individuals, or an overall incidence of approximately 1.2 per 10,000 population starting haemo- or peritoneal dialysis (Kramer et al. 2019). However, most patients receiving dialysis are not eligible for a kidney transplantation. 20,165 individuals were registered on waiting-lists for kidney transplantation in 2018 (EDQM 2019). As an approximation, 15% of the listed patients can be expected to be highly sensitized, which would correspond to approximately 3,025 highly sensitized individuals being listed in Europe per year (0.0006 per 10,000 population).

Prevalence

Based on ERA-EDTA registry data, 564,638 individuals were treated for ESRD on 31-Dec-2016, corresponding to an overall unadjusted prevalence of 8.2 per 10,000 population. If excluding the 37% of these patients who were living with a kidney transplant, approximately 356 000 individuals were on dialysis (58% of the total received haemodialysis and 5% received peritoneal dialysis), (Kramer et al. 2019). As an approximation, 15% of these can be expected to be highly sensitized (Iyer et al. 2013), which would correspond to approximately 53,000 highly sensitized individuals receiving dialysis in Europe.

The number of patients on the waiting-list for a kidney transplant (only active candidates) on 31-Dec-2018 was 47,788 in the European countries included in the EDQM report (EDQM 2019). As an approximation, 15% of these (7,200 patients) can be expected to be highly sensitized (Iyer et al. 2013). Based on a European population of 510 million inhabitants (EDQM 2019) , the prevalence of highly sensitized patients in Europe who are otherwise eligible for kidney transplantation would be approximately 0.001 per 10,000 inhabitants.

Approximately 35% of the highly sensitized patients with PRA>85% have a very low likelihood of ever receiving a compatible kidney transplant (EUROSTAM 2018), and these patients are currently estimated to approximately 2,500 in the EU.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age, Gender and Ethnicity

Demographic data specifically on highly sensitized patients in Europe, who are otherwise eligible for kidney transplantation, have not been found. This section therefore mainly presents demographic data on patients in Europe treated for ESRD (i.e. receiving haemo- or peritoneal dialysis, or kidney transplantation), irrespective of sensitization status, complemented with US data on highly sensitized patients.

According to the ERA-EDTA Registry annual report 2016, based on datasets from 52 national or regional renal registries in 34 European countries covering a general population of 677 million, 564,638 individuals were treated for ESRD on 31-Dec-2016, corresponding to an overall unadjusted prevalence of 8.2 per 10,000 population (Kramer et al. 2019). The mean age was 63.1 years (median: 65.8 years). When analysing the data by age category, 1% were paediatric patients (0-19 years), 47% were 20-64 years and 52% were elderly (65-74 years: 25%; >75 years: 27%). Almost two-thirds (62%) were men (ERA-EDTA 2016).

Similarly, among 23,530 patients included in the Collaborative Transplant Study (CTS) database who received deceased-donor kidney transplants in Europe in 2005-2008, 3.6% of patients were 0-17 years, 6.3% were 18-29 years, 12.6% were 30-39 years, 20.9% were 40-49 years, 27.5% were 50-59 years and 29.1% were 60 years or above (Gondos et al. 2013). In the same database, the proportion of non-white patients was very low: of the 52,461 patients entered into the clinical analysis in 2000-2008, only 1,000 were known to be non-whites, of whom 562 (1.1% of the total) were known to be of African origin. Note that, for some registries in Europe, legal constrains forbid the registration of recipient ethnicity (Gondos et al. 2013).

Demographics by presence of donor-specific antibodies (DSAs)

In a population-based study analysing 1,016 kidney recipients at 2 centres in Paris in 2005-2010 (Loupy et al. 2013), the mean age was 47.6 years (standard deviation: 13 years) and was almost identical among patients with (N=316) and without (N=700) DSAs. Overall, 59% of the recipients were

men. The percentage of women with DSAs (37%; 153 of 417) was slightly higher than the percentage of men (27%; 163 of 599) with DSAs (Loupy et al. 2013).

In an analysis of the United Network for Organ Sharing (UNOS) dataset comprising all kidney transplants in the US between 1997 and 2014, highly sensitized kidney transplant recipients (PRA of ≥98%; N=7,145) were younger (46.7 ± 12.3 years vs 50.5 ± 13.7 years, p<0.001), more frequently female (62.7% vs 31.8%, p<0.001) and more likely to be African American (29.6% vs 22.6%, p<0.001) compared with non-sensitized kidney-transplant recipients (N=100,147), (Redfield et al. 2016). The higher percentage of female patients among highly sensitized patients may reflect that pregnancy contributes to sensitization.

Risk Factors

- Risk factors associated with accelerated worsening of chronic kidney disease (CKD), i.e. decline in glomerular filtration rate (GFR) include:
    - Type of kidney disease: diabetic kidney disease, glomerular disease, and polycystic kidney disease
    - Nonmodifiable patient characteristics: African American ethnicity, lower baseline level of kidney function, male gender, older age
    - Modifiable patient characteristics: proteinuria, low serum albumin, hypertension, glycaemic control in diabetes, smoking
- Cardiovascular risk factors in CKD:
    - Heart failure, recent myocardial infarction, angina pectoris, arrhythmias, left ventricular hypertrophy, cerebrovascular disease, peripheral vascular disease. Risk factors for cardiovascular disease include; diabetes, dyslipidaemia, obesity, smoking.

  Source: K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (KDOQI 2004).
- Risk factors associated with formation of DSAs:
    - Exposure to foreign antigens occurring during pregnancy, blood transfusions, infections and organ transplantation (Stites et al. 2015; Thomas et al. 2015)
- Risk factors associated with AMR:
    - Pre-existing DSAs and/or a positive crossmatch, or development of *de novo* DSAs in patients without DSAs at transplantation (Kissmeyer-Nielsen et al. 1966; Montgomery et al. 2004; Terasaki et al. 2005).

The main existing treatment options:

Main existing pre-treatment options for desensitization

Renal transplantation is the optimal treatment for patients with CKD stage 5, also called end-stage renal disease (ESRD) since it increases patient survival and quality of life and is cost effective compared to continuing dialysis (Montgomery et al. 2005; Montgomery et al. 2011; Vo et al. 2013; Orandi et al. 2014; Orandi et al. 2016).

There is no standardised or approved protocol for desensitisation but a few centre-specific local protocols have been developed to make some sensitized patients eligible for transplantation (Jordan et al. 2015; Vo et al. 2008). These protocols use procedures to remove antibodies, e.g. plasmapheresis or immunoabsorption often combined with B-cell depleting agents, e.g. rituximab and bortezomib,

immune-modulatory agents, e.g. IV IgG (IVIg) (Vo et al. 2008; Montgomery et al. 2000), or complement blockers, e.g. eculizumab (Jordan et al. 2015; Djamali et al. 2014). These treatments require repeated dosing for several weeks or months prior to transplantation and are mainly used for living-donor kidney transplantations since deceased-donor organ transplantations must occur within hours of death of the donor to reduce the risk of delayed graft function and allograft loss (Terasaki et al. 2005). Many patients do not respond to these regimens with the required reduction in antibody levels to enable transplantation, especially if the antibody levels are very high.

Without desensitization treatment, it is difficult to find an acceptable donor for sensitized patients. Therefore, the highly sensitized patients have an extended waiting time for transplantation and are less likely to ever receive a transplant. Prolonged waiting time is associated with a greater likelihood of death (Iyer et al. 2013; Orandi et al. 2016). In 2018, 1,911 patients died while being on the kidney transplant waiting-list in Europe (EDQM 2019).

Post-transplant care following imlifidase vs post-transplant care in patients not treated with imlifidase

There is no standardised or approved protocol for desensitization. However, as discussed above, some centres have developed and tested protocols suitable for living donor transplantations using techniques to lower antibody levels, either through high-dose IVIg or plasmapheresis/immunoadsorption often combined with low-dose IVIg (Vo et al. 2008; Montgomery et al. 2000).

Table SI.1 summarises differences in the care of imlifidase-treated kidney-transplanted patients compared with the standard of care of non-sensitized and sensitized patients in general kidney transplantation.

The care of kidney-transplanted patients treated with imlifidase is consistent with the standard of care for other sensitized kidney transplant patients with a few exceptions;

- Patients should be treated with an oral antibiotic agent, covering bacteria causing respiratory tract infections, to prevent infections in the absence of IgG.
- Rabbit ATG is not recommended the first week after imlifidase since it is effectively cleaved by imlifidase (equine ATG or alemtuzumab can be used).
- Alemtuzumab is to be administered at the earliest 4 days after imlifidase to prevent cleavage of the antibody.

Table SI.1: Standard of care in general kidney transplantation (non-sensitized patients and sensitized patients) vs care of imlifidase-treated transplanted patients

	Non-sensitized patients	**Sensitized patients**	**Imlifidase-treated patients**
Premedication	Standard of care is not established, i.e. use of premedication with corticosteroids and antihistamines varies across transplant centres. Patients treated with T-cell-depleting agents are given premedication with corticosteroids and antihistamines before infusion.		Premedication with corticosteroids and antihistamines should be given before imlifidase infusion to reduce the risk of infusion-related reactions.
Immunosuppression (induction therapy)	KDIGO guidelines recommend a combination of immunosuppressive medications starting before, or at the time of, kidney transplantation and	Recipients at higher immunological risk may be considered for T-cell (lymphocyte) depleting antibodies (Baker et al. 2017).	As standard of care of immunologic high-risk patients; but note that while equine ATG or alemtuzumab can be used, rabbit ATG is not recommended the first week after imlifidase infusion since it is efficiently

	Non-sensitized patients	**Sensitized patients**	**Imlifidase-treated patients**
	induction therapy with a biologic agent as part of the initial immunosuppressive regimen (KDIGO 2009).	Induction therapy using steroids and ATG, anti CD52 (e.g. alemtuzumab) and/or anti-IL2R antibody (e.g. basiliximab) to prevent acute cellular rejections (Sandal et al. 2019).	cleaved by imlifidase. Alemtuzumab can be administered at the earliest 4 days after imlifidase. If alemtuzumab is used as induction therapy on Day 4, pulse steroid treatment can be used up to Day 4 to prevent T-cell-mediated rejection. IVIG (Day7) and rituximab (Day 9) were given in some, but not all, clinical studies with imlifidase.
Immunosuppression (initial maintenance immunosuppression)	A combination of immunosuppressive medications as maintenance therapy including a calcineurin inhibitor (tacrolimus as the first-line calcineurin inhibitor, started before or at the time of transplantation) and an antiproliferative agent (MMF as the first-line antiproliferative agent) and corticosteroids (KDIGO 2009).	Immunologic high-risk patients (transplant recipients who have rejected one or more transplants aggressively, i.e. within the first year post transplantation, or any recipient with > 80% PRA) receive calcineurin inhibitor, prednisone, and MMF (BC Transplant. Clinical Guidelines for Kidney Transplantation 2018).	No difference from standard of care of sensitized patients.
Immunosuppression (long-term maintenance immunosuppression)	Lowest planned doses of maintenance immunosuppressive medications by 2–4 months after transplantation, if there has been no acute rejection. Calcineurin inhibitors to be continued rather than withdrawn (KDIGO 2009). Prednisone to be continued rather than withdrawn if being used beyond the first week after transplantation (KDIGO 2009). Patients remain on immunosuppression for the life of their transplanted kidney. The goal is to minimize immunosuppressive side effects and	Slower tapering of the calcineurin inhibitor and life-long treatment with corticosteroids, MMF and calcineurin inhibitor.	No difference from standard of care or sensitized patients.

	Non-sensitized patients	Sensitized patients	Imlifidase-treated patients
	complications balanced with providing enough immunosuppression to prevent transplant rejection. Generally, immunosuppressive dose reductions may begin after 3 months (BC Transplant. Clinical Guidelines for Kidney Transplantation 2018).		
Antibiotics		No established standard of care but reported use of an oral antibiotic for at least 1 week (oral communication).	An oral antibiotic agent covering bacteria causing respiratory tract infections is added to reduce the potentially increased risk of such infections as these are the most common in patients with hypogammaglobulinemia.
	A single dose of IV broad spectrum antibiotics, e.g. a cephalosporin, to prevent surgical site infections (Bachmann et al. 2019).	No differences from standard of care.	
	Daily oral doses of oral trimethoprim sulfamethoxazole as *Pneumocystis carinii* (jiroveci) prophylaxis as well as prophylaxis against urinary tract infection for 6 months (KDIGO 2009).	No differences from standard of care.	
	Viral prophylaxis against CMV for at least 3 months after transplantation (KDIGO 2009).	No differences from standard of care.	
	Prophylaxis against oral candida for 1–3 months after transplantation (KDIGO 2009).	No differences from standard of care.	
Duration of hospitalisation	Wide variation	Due to the need for increased monitoring of immunological events and treatment of any rejection episode, the duration of hospitalisation is often longer in sensitized than non-sensitized patients.	

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Chronic kidney disease (CKD) stage 5 or end-stage renal disease (ESRD)

CKD stage 5 (also called ESRD) is the most severe grade (advanced stage) of CKD. Untreated, ESRD results in death. The treatment options for patients with ESRD include dialysis and kidney transplantation. Renal transplantation is the optimal treatment for patients with kidney failure since it

increases patient survival and quality of life and results in substantial savings in health care costs compared to continued dialysis (Montgomery et al. 2005; Montgomery et al. 2011; Vo et al. 2013; Orandi et al. 2014; Orandi et al. 2016).

ESRD is associated with increased mortality compared to age-matched controls. Increasing age, diabetes, cardiovascular disease and poor nutrition are the most important co-existing conditions predicting worse outcomes for patients with ESRD. Hypertension can be both a cause of renal failure and a frequent complication of renal insufficiency. Hypertension is a predisposing factor for the development of left ventricular hypertrophy, which is a risk factor for both the development of congestive heart failure and death. Ischemic heart disease has been reported in 40% to 60% of dialysis patients and left ventricular hypertrophy has been reported in up to 75% of patients on haemodialysis or peritoneal dialysis. There are multiple risk factors associated with uraemia that predispose to these conditions. Although hypertension in the general population is associated with higher mortalities, hypotension is a more accurate predictor of high mortality rates in dialysis patients. Diabetes is the most common cause of ESRD in many parts of the world. It has a strong negative impact on survival and is associated with the presence of vascular disease. Poor nutritional status, as indicated by a low serum albumin or subjective global assessment is a strong predictor of high mortality. However, low serum albumin levels may in part also indicate the coexistence of a chronic inflammatory state. Overall, the most important predictors of poor outcome in ESRD are increasing age, cardiovascular disease, diabetes and poor nutrition as reflected by hypoalbuminemia (Prichard 2000).

Major challenges in kidney transplantation

Two of the major challenges in kidney transplantation are the long mean waiting time to transplantation and the risk for allograft rejection. Allograft rejection can be T-cell-mediated and/or antibody-mediated rejection (AMR). T-cell-mediated rejection is a common form of early rejection and is the target of maintenance immunosuppressive treatment. AMR can cause immediate (hyperacute), early (active and chronic active AMR) or chronic changes (chronic AMR) and transplantation is avoided in patients at high risk for AMR. In AMR, preformed or acquired antibodies may lead to destruction of the allograft.

Humoral sensitization to HLA antigens and ABO systems remain one of the largest barriers to further expansion in renal transplantation. This barrier translates into prolonged waiting times and a greater likelihood of death. The number of highly sensitized patients on the renal transplant waiting-list continues to increase. Desensitization protocols to remove antibodies, kidney-paired donation programmes (to circumvent antibodies) or a combination of both have broadened the access to transplantation for some of the patients who are disadvantaged by immunologic barriers if they have access to a living donor (Iyer et al. 2013).

Another challenge in kidney transplantation is infections, which are very common in this patient population (Naik et al. 2016) due to the underlying renal disease, surgery, hospitalisation and especially the immunosuppressive treatment.

Development of anti-HLA antibodies and transplantation waiting time

As mentioned above, approximately one third of patients waiting for kidney transplantation are sensitized to potential donor tissues, i.e. they have anti-HLA antibodies (Iyer et al. 2013). HLA antibodies arise due to exposure to foreign antigens occurring during pregnancy, blood transfusions, infections and previous organ or cell transplantations (Stites et al. 2015; Thomas et al. 2015). A patient with antibodies against a potential donor, i.e. DSAs, will result in a positive crossmatch test against that donor. It can be very difficult to find an acceptable donor for patients with antibodies reacting against a wide range of HLAs resulting in less likelihood to receive a kidney transplant and a

greater likelihood of death (Iyer et al. 2013). Sensitized patients have an extended waiting time to transplantation, and a study conducted in the UK showed that the waiting time increased from 788 days for patients with no or low grade of sensitization to 2232 days (>6 years) for highly sensitized patients (Orbach et al. 2005). During 2018, 1,911 patients in Europe died while being on the kidney transplant waiting-list (EDQM 2019), however, the sensitization status for these patients is not reported. In the US, a higher percentage of highly sensitized patients died while on the waiting-list compared with non-sensitized patients (17.3% vs 11.6%, p<0.001), (Redfield et al. 2016).

Antibody-mediated rejection (AMR)

For kidney transplant patients, DSAs are associated with an increased incidence of acute and chronic AMR, which is a risk factor for shorter long-term graft survival. The frequency of AMR in highly sensitised patients desensitised with imlifidase (31%) is similar to the frequencies reported in the literature (25-61%) for sensitised patients being desensitised and transplanted (Lefaucheur et al. 2008; Magee et al. 2008; Thielke et al. 2009; Gloor et al. 2010; Haririan et al. 2009; Riella et al. 2014; Vo et al. 2008). Notably, literature data include living-donor kidneys, which generally have a better outcome than deceased-donor organs. The pathophysiology of AMR suggests a primary role for antibodies, B-cells and plasma cells. It has been suggested that plasma cells produce DSAs that interact with the endothelium, which activates the cellular pathways responsible for the development of microcirculatory changes and tissue injury (Djamali et al. 2014).

Treatment of allograft rejection

KDIGO clinical practice guidelines (KDIGO 2009) recommend treatment with high dose corticosteroids for the initial treatment of acute cell-mediated rejection. Use of lymphocyte-depleting antibodies is suggested for treatment of acute cell-mediated rejections that do not respond to corticosteroids, and for recurrent acute cell-mediated rejections. Further, KDIGO clinical practice guidelines suggest treatment of acute AMR with one or more of the following alternatives, with or without corticosteroids; plasma exchange, immunoadsorption, IVIg, anti-CD20 antibody and lymphocyte-depleting antibody (KDIGO 2009). More recently introduced therapies include the complement C5-inhibitor eculizumab (Susal et al. 2011) and the proteasome inhibitor bortezomib (Abbas et al. 2019). However, no current therapy is approved for the treatment of AMR.

Graft loss and return to dialysis

Untreated acute rejection inevitably results in graft destruction (KDIGO 2009). Also, subclinical AMR, which is a frequent finding in patients with preformed HLA-DSAs, is associated with worse GFR at 1 year after transplantation (Lefaucheur et al. 2010; Djamali et al. 2014). Progressive lesions lead to chronic AMR and are recognized to be a distinct cause of late graft dysfunction and loss (Lefaucheur et al. 2010; Djamali et al. 2014). Graft failure and return to dialysis also have emotional consequences for the patients and costs for the health care system (Gloor et al. 2008; Haas et al. 2014; Jordan et al. 2010; Lefaucheur et al. 2010; Port et al. 1993; Reinsmoen et al. 2008; Hart et al. 2018).

Mortality

Based on ERA-EDTA registry data, the unadjusted 5-year survival probability was 42.1% (95% CI: 42.0%-42.3%) for patients on dialysis vs 87.7% (95% CI: 87.3%-88.0%) after a first kidney transplantation with a graft from a deceased donor (Kramer et al. 2019).

The mortality hazard ratio (HR) compared to matched general population controls has been reported to be 5.6 (95% confidence interval [CI]: 3.5-8.9) for transplanted patients, 9.2 (95% CI: 6.6-12.7) for patients receiving peritoneal dialysis and 12.6 (95% CI: 10.8-14.6) for patients receiving haemodialysis (Neovius et al. 2014).

Important co-morbidities:

Kidney disease is associated with a large number of comorbidities:

- Cardiovascular disease and dyslipidaemia
    - Hypertension is both a cause and a complication of CKD and is associated with adverse outcomes, in particular faster loss of kidney function and development of cardiovascular disease (K/DOQI 2002).
    - Cardiac abnormalities including left ventricular hypertrophy, left ventricular dilatation, arterial aortic stiffening, coronary atherosclerosis with calcification, myocardial infarction and congestive heart failure (Foley et al. 1995; Pannier et al. 2005; Schwarz et al. 2000).
    - Patients with CKD are at increased risk of cerebrovascular disease and peripheral vascular disease (K/DOQI 2002).
    - Patients treated with chronic haemodialysis have 10 to 20-fold higher risk of death from cardiovascular disease compared to the general population, and overall decreased long-term survival (Levey et al. 1998; Montgomery et al. 2011).
- Anaemia (K/DOQI 2002).
- Malnutrition (protein energy malnutrition) (K/DOQI 2002).
- Mineral (calcium and phosphorus metabolism) and bone disorders:
    - Secondary hyperparathyroidism may lead to osteoporosis and fractures.
    - Hypocalcaemia may lead to paraesthesia, bronchospasm, laryngospasm, tetany and seizures (K/DOQI 2002).
- Impaired well-being and impaired functional status (K/DOQI 2002).
- Neuropathy (K/DOQI 2002).
- Diabetic complications: The risk of cardiovascular disease, retinopathy, and other diabetic complications is higher in patients with diabetic kidney disease than in diabetic patients without kidney disease (K/DOQI 2002).

Part II: Module SII - Non-clinical part of the safety specification

Introduction

The non-clinical programme with imlifidase comprises 11 toxicity studies, the scopes of which are summarized in Table SII.1. As indicated in the Table, two drug product formulations with different drug substance materials (Process 1 and Process 2 materials, the latter intended for marketing) have been used in these studies. Where a comparison between studies can be made, no difference in the toxicity of the two formulations has been identified.

Table SII.1: Summary of safety studies within the non-clinical programme for imlifidase

Study Number	Species	Scope of study					
		Single dose	Repeated dose	Local tolerance	Embryofoetal development	Safety pharmacology	GLP
2012-035	NZW Rabbits	X	X	-	-	-	No
2018-042R	*NZW Rabbits*	X	-	-	-	-	No
2012-007	Beagle Dogs	X	X	-	-	X	No
2016-062	NZW Rabbits	-	X	-	-	-	No
2016-003	NZW Rabbits	-	X	-	-	-	No
2012-006	NZW Rabbits	-	X	-	-	-	No
2012-011[1]	NZW Rabbits	-	X	X	-	-	Yes
2018-075R	*NZW Rabbit*	-	X	-	-	-	Yes
2012-012[2]	Beagle Dogs	-	X	X	-	X	Yes
2017-004R	*NZW Rabbits*	-	-	-	X	-	No
2017-181R	*NZW Rabbits*	-	-	X	X	-	Yes

[1] Supported by supplemental anti-drug antibody (ADA) analysis in study 2012-031
[2] Supported by supplemental ADA analysis in study 2012-030
Studies shown in italics were conducted with the final lyophilized formulation containing Process 2 material.

Imlifidase shows full enzymatic activity on IgG from human and rabbit whereas no, or only partial cleavage, was seen on IgG from dog and other tested species, including primates. In Beagle dog, imlifidase is capable of cleaving some but not all IgG subclasses into $F(ab')_2$ and Fc-fragments. Therefore, the rabbit was considered as the most relevant species to evaluate the toxicity of imlifidase. However, some early studies were conducted in Beagle dogs before the imlifidase cleavage capacity in this species was fully understood.

No genotoxicity studies have been performed since it is not expected that biotechnology-derived pharmaceuticals will interact directly with DNA or other chromosomal material (ICH-S6(R1) 2011). Due to the nature of the molecule as a bacterial enzyme and the intended single-dose administration, no studies on carcinogenicity have been performed (ICH-M3(R2) 2009).

The toxicity to reproduction package for imlifidase is abridged when compared to ICH M3(R2) recommendations, as women of child bearing potential should refrain from becoming pregnant for a period of at least 6 months after transplantation (Shah et al. 2016). Furthermore, use of imlifidase in pregnant women is not applicable since pregnancy is a contraindication to kidney transplantation in general.

No dedicated safety pharmacology studies have been performed, but functional effects on the cardiovascular and respiratory systems were evaluated as part of both studies performed in dogs.

The information summarized here describes the key safety findings from non-clinical studies and relevance to human usage.

Vascular system

Peri-/arteritis

In 2 females of the high-dose (20 mg/kg) group of the pivotal repeat-dose study with Process 1 material in the rabbit, minimal to moderate peri-/arteritis dominated by interstitial heterophilic granulocytes was recorded in several organs. The affected organs included, but were not restricted to, meninges of the brain and spinal cord, lungs, kidneys, liver, urinary bladder, reproductive organs, and adnexal tissue of several organs. No peri-/arteritis was seen in animals allowed a recovery period of 29 days.

All animals developed ADAs in this study, however, the ADA levels found in the 2 animals with peri-/arteritis were in the higher range and it cannot be excluded that immune complex formation and deposition was responsible for the peri-/arteritis seen. Peri-/arteritis was not observed in the pivotal repeat-dose study in rabbits with Process 2 material, where the highest dose investigated was 12 mg/kg, i.e. somewhat lower than the maximal dose of 20 mg/kg investigated with the Process 1 material.

Also, 1 dog in the high-dose (20 mg/kg) group of the pivotal study in this species developed an inflammatory reaction in multiple organs; this was, however, considered due to Beagle pain syndrome.

Histological changes in the myocardium

Histopathological changes in the myocardium were seen in all rabbit dose groups (0.2, 2 and 12 mg/kg) receiving 4 administrations of Process 2 material. Minimal to slight myocardial cell degeneration associated with fibroblasts and minimal to moderate inflammatory cells infiltration were noted in the right ventricle only, extending through the chamber wall. These changes were completely reversible within a 4-week recovery period. A re-read of the heart slides from the initial GLP-compliant repeat-dose study conducted with the Process 1 material showed heart changes similar to those observed with the Process 2 material. Importantly, no changes were seen in animals which received 2 treatments of 2 mg/kg, indicating that multiple treatment is necessary to induce these changes.

Lung

Increase in alveolar macrophages/perivascular inflammatory cell infiltration

An increased incidence and distribution of alveolar macrophages (minimal to slight) were seen in the high-dose group (20 mg/kg) of the pivotal 4-week repeat-dose study in rabbits investigating the Process 1 material. These changes were considered an exacerbation of a common background finding in the rabbit lung. Alveolar macrophages and perivascular inflammatory cell infiltration were present in the lung of all dose groups in the 4-week repeat dose rabbit study investigating the Process 2 material. Although the perivascular cell infiltration was observed in both control and treated animals, there appeared to be a weak dose relationship in severity of the finding. No apparent differences in this diagnosis were observed between controls and rabbits administered 2 doses of 2 mg/kg imlifidase.

It is unlikely that the increase in alveolar macrophages or the perivascular cell infiltration was related to removal of IgG, or the generation of $F(ab')_2$ and Fc fragments. Generation of IgG fragments occur within 5 minutes post dosing and full effect was observed with all administered doses. It is also unlikely that the increase in alveolar macrophages was immune complex-mediated, as it was seen already 72 hours post dosing in two investigative studies. No animals had pre-formed ADAs or detectable ADAs at this time point. It is also unlikely that the increase in perivascular inflammatory cell infiltration was immune complex-related since 9 of 10 control rabbits showed this change. Animals at all dose levels (from 0.2 to 20 mg/kg) were administered high doses of imlifidase intravenously over 1 minute. Large amounts of substance passing the lungs in a short period may have resulted in a potential deposition, leading to increased perivascular inflammatory cell infiltration or alveolar

macrophage uptake/activation. Importantly, the changes were reversible, did not result in any clinical signs and no treatment-related lung changes were observed in rabbits administered 2 doses of 2mg/kg of Process 2 material.

Kidney

Tubular basophilia and focal interstitial fibrosis in the cortex of the kidneys were recorded in 3/6 dogs administered 2 doses of 20 mg/kg of the Process 1 material (1 of these showing pathology resembling Beagle pain syndrome). No changes were observed in kidney-related laboratory parameters. Tubular basophilia is a commonly occurring background change in dogs, and it could not be excluded that the recorded findings represented a treatment-related exacerbation of the background findings.

Among the 3 dogs with kidney findings, 2 had detectable levels of ADA prior to the second dosing, as did 1 animal without kidney findings. 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. No infiltration of inflammatory cells was recorded. Considering the pharmacokinetics of imlifidase in dogs at 20 mg/kg ($t_{½}$=13 hours), immune complexes are not likely to have been formed until the second dosing (Day 8). Also, the animals were sacrificed 3 days after the 2nd dosing (Day 11) and, thus, it is unlikely that immune complex-mediated injuries could have presented with interstitial fibrosis within this short time frame.

No treatment-related renal changes were recorded in the recovery animals.

Immune system

No infusion-related reactions were observed in the pivotal repeat-dose and embryofoetal toxicity studies in rabbits. Anaphylactic shock-resembling reactions during infusion were observed in 2 dogs receiving repeated injections of imlifidase in a pilot toxicity study. The reactions occurred in connection with the 3rd dose and slowly resolved after dexamethasone treatment.

No correlation has been established between ADA levels and clinical signs in the pivotal rabbit and dog toxicity studies, however, due to the small number of animals, it cannot be excluded that immune complex formation and deposition can occur.

The intended pharmacological effect upon treatment with imlifidase is reduction of IgG levels. This was seen in both rabbit and dog at all investigated dose levels but did not result in infections in any of the animals.

Haematological effects:

A dose-dependent increase in fibrinogen was seen in rabbits of both sexes after repeated treatment in the study where the Process 1 material was investigated, but not after single-dose treatment. Besides its role in haemostasis, fibrinogen acts as an acute phase protein in inflammatory and tissue repair processes. The increase of fibrinogen in rabbits is likely an acute phase response to repeat injections of a non-self protein such as imlifidase.

Conclusion

None of the non-clinical safety findings described above warrants further non-clinical studies.

The infusion-related anaphylactic shock-resembling reactions (seen after a third injection in the dog), tubular basophilia and fibrosis were the only treatment-related toxicities observed after 2 once weekly IV doses of 20 mg/kg. No kidney changes were seen in dogs allowed a recovery period of 29 days, or in dogs administered 0.2 mg/kg or 2 mg/kg (NOAEL). The intended human dose is 0.25 mg/kg. Thus, these kidney findings are not considered to pose a risk when imlifidase is used clinically as a single IV dose.

Repeat-dose studies in rabbits showed reversible myocardial cell degeneration associated with fibroblasts and inflammatory cell infiltration in the right ventricle in all dose groups receiving 4 once weekly injections of imlifidase. The origin of these heart findings has not been identified. No heart findings were observed in rabbits administered 2 once weekly administrations with 2 mg/kg.

Infusion-related reactions may be considered an important identified or potential risk. Furthermore, although no infections were seen in the non-clinical studies, the intended mechanism of imlifidase is reduction of IgG levels, which may increase the risk of infections.

Part II: Module SIII - Clinical trial exposure

The clinical programme with imlifidase for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor, comprises 6 prospective clinical studies, whereof 2 in healthy men (11-HMedIdeS-01 and 18-HMedIdeS-15) and 4 in patients with CKD stage 5 (ESRD) (studies 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06). In addition, a long-term (5-year) follow-up study of patients treated with imlifidase in the above-mentioned studies in CKD has been completed (study 17-HMedIdeS-14), Table SIII.1a.

Table SIII.1a: Summary of clinical studies within the clinical programme for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor

Study	Population	Exposure Dose (administered IV)	Duration of follow-up in the core study
11-HMedIdeS-01	Healthy, male subjects	No. of subjects exposed: N=20 - Single dose of 0.010 mg/kg: N=8 - Single dose of 0.040 mg/kg: N=4 - Single dose of 0.12 mg/kg: N=4 - Single dose of 0.24 mg/kg: N=4	64 days
13-HMedIdeS-02	Patients with CKD	No. of subjects exposed: N=8 - 2 doses of 0.12 mg/kg: N=3 - Single dose of 0.25 mg/kg: N=3 - 2 doses of 0.25 mg/kg: N=2	64 days
13-HMedIdeS-03	Patients with CKD	No. of subjects exposed: N=10 - Single dose of 0.25 mg/kg: N=5 - Single dose of 0.50 mg/kg: N=5	180 days
14-HMedIdeS-04	Patients with CKD	No. of subjects exposed: N=17 - Single dose of 0.24 mg/kg: N=17	180 days
15-HMedIdeS-06	Patients with CKD	No. of subjects exposed: N=19 - Single dose of 0.25 mg/kg: N=16 - 2 doses of 0.25 mg/kg: N=3	180 days
17-HMedIdeS-14	Prospective, observational long-term (5-year) follow-up of patients with CKD treated with imlifidase in previous studies, i.e. this study does not represent any new patients but provides information regarding long-term outcomes.		
18-HMedIdeS-15	Healthy, male subjects	No. of subjects exposed: N=15 - Single dose of 0.25 mg/kg: N=15	64 days

In addition, complementary crossmatch and AMR data were retrospectively collected in study 17-HMedIdeS-13 for patients treated with imlifidase in studies 13-HMedIdeS-02 and 13-HMedIdeS-03. This study is not included in the table above since no new patients were enrolled and this was not an interventional study.

89 subjects (54 patients with CKD and 35 healthy men) have received imlifidase in studies within the programme for the indication desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor, Table SIII.1b.

46 of the 54 patients with CKD (85%) received a single IV dose of imlifidase and 8 (15%) received 2 IV doses, Table SIII.1c. The maximum total dose administered was 0.50 mg/kg (N=10; administered as a 0.50 mg/kg single dose in 5 patients and as 2 doses of 0.25 mg/kg in 5 patients). Patients who received 2 doses had the doses separated by 11.6 to 30.8 hours, with the exception of 1 patient who received 1 dose of 0.25 mg/kg in study 13-HMedIdeS-02 (treated but not transplanted in this study) and 1 dose of 0.50 mg/kg in study 13-HMedIdeS-03 (treated and transplanted in the latter study). Based on the long interval between the 2 dosing occasions (1.5 years) in this patient and since the IgG values reverted to normal between the studies, this patient is counted twice, i.e. as if receiving 1 dose in each study. No patients have received more than 2 doses.

Table SIII.1b shows exposure data for all 54 patients with CKD within the core study (updated data now available in Table SIII.1c). The total follow-up duration until the end of the core studies corresponded to 23.1 subject-follow-up-years.

Patients with CKD who were treated with imlifidase and transplanted in studies 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 or 15-HMedIdeS-06 were asked to participate in study 17-HMedIdeS-14 for long-term (5-year) follow-up. Table SIII.1c shows exposure data up to 12 months with the DLP for cumulative data of 01-Dec-2019.

At DBL for this RMP, study 17-HMedIdeS-14 has been completed with database lock on 28 April 2023, and the clinical study report is dated 27 October 2023.

Table SIII.1b: Number of subjects exposed, number of IV infusions and cumulative duration of follow-up after exposure to imlifidase by population (patients with CKD/healthy volunteers) within the clinical programme for the indication 'desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor'

		Patients with CKD (N=54)	Healthy volunteers (N=35)
Number of infusions	n	54	35
	1	46 (85.2%)	35 (100%)
	2	8 (14.8%)	[a]
Cumulative duration of follow-up after treatment - until the end of the core study	1 month	53 (98.1%)	35 (100%)
	3 months	44 (81.5%)	
	6 months*	25 (46.3%)[b]	

*6 months was defined as at least 180 days
Note: This table shows the duration of follow-up and not the duration of exposure since imlifidase is intended to be administered as a single dose
[a] Only preliminary 1-month data available for healthy volunteers in Study 18-HMedIdeS-15 (i.e. 2-month data not available at the DLP for this table).
[b] Patients having the 6-month visit before Day 180 are not included as having 6-month follow-up data in this table (see Table SIII.1c for additional 6- and 12-month follow-up data.)
Data lock point (DLP) for this table: 01-Dec-2019
Source: Data extracted from Module 5.3.5.3 Table 1.2.2.3

Table SIII.1c: Number of subjects exposed and cumulative duration of follow-up after exposure to imlifidase, by total dose in transplanted patients with CKD

	Months	**0.25 mg/kg (N=38) n (%)**	**0.50 mg/kg (N=8) n (%)**	**Total (N=46) n (%)**
Cumulative duration of follow-up after treatment (months) - until the last contact	6	38 (100.0)	8 (100.0)	46 (100.0)
	12	33 (86.8)	6 (75.0)	39 (84.8)

Note: 6 months: ≥180 days; 12 months: ≥365 days
This table shows the duration of follow-up and not the duration of exposure since imlifidase is intended to be administered as a single dose
Patients who received 1 dose of 0.24 mg/kg or 2 doses of 0.12 mg/kg are included in the 0.25 mg/kg dose group.
DLP for cumulative data for this table: 01-Dec-2019

The mean age of the 54 patients with CKD (27 men and 27 women) who have received imlifidase in completed studies within this programme was 43.8 years (range: 20 to 73 years), Table SIII.2. Three patients (6%) were 65 years or above, Table SIII.2. 43 patients (80%) were 'White', 4 (7%) were 'Black or African American' and 7 (13%) were of 'Other' origin, Table SIII.3.

Table SIII.2: Demographics: age, age group, weight, BMI and BMI category by gender (patients with CKD, safety set) within the clinical programme for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor

Demographic characteristics			Female (N=27)	Male (N=27)	Total (N=54)
Age (years)	N		27	27	54
	Mean (SD)		44.2 (12.8)	43.3 (13.7)	43.8 (13.1)
	Median		46.0	41.0	44.5
	Min; Max		20; 73	20; 69	20; 73
Age group (years)	Paediatric individuals:	<18 years	0	0	0
	Adults	18-64 years	26 (96.3%)	25 (92.6%)	51 (94.4%)
	Elderly people:	65-74 years	1 (3.7%)	2 (7.4%)	3 (5.6%)
		>74 years	0	0	0
Weight (kg)	N		27	27	54
	Mean (SD)		65.9 (16.6)	76.6 (13.8)	71.3 (16.1)
	Median		67.0	75.1	71.9
	Min; Max		31; 96	45; 107	31; 107
BMI (kg/m^2)	N		27	26	53
	Mean (SD)		24.3 (5.1)	25.0 (4.0)	24.6 (4.6)
	Median		24.3	24.0	24.0
	Min; Max		13; 37	18; 34	13; 37
BMI category (kg/m^2)	<18.5		2 (7.4%)	1 (3.8%)	3 (5.7%)
	18.5-<25		14 (51.9%)	13 (50.0%)	27 (50.9%)
	25-<30		8 (29.6%)	9 (34.6%)	17 (32.1%)
	>=30		3 (11.1%)	3 (11.5%)	6 (11.3%)

Source: Data extracted from Module 5.3.5.3 Table 1.3.1

Table SIII.3: Ethnic origin by gender (patients with CKD, safety set) within the clinical programme for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor

Demographic characteristics		Female (N=27)	Male (N=27)	Total (N=54)
Race	N	27	27	54
	White	22 (81.5%)	21 (77.8%)	43 (79.6%)
	Black	2 (7.4%)	2 (7.4%)	4 (7.4%)
	Other	3 (11.1%)	4 (14.8%)	7 (13.0%)
Ethnicity	N	27	27	54
	Not Reported	27 (100%)	27 (100%)	54 (100%)

Source: Data extracted from Module 5.3.5.3 Table 1.3.1

Other Baseline Characteristics of Transplanted Patients

39 of the 46 patients (85%) transplanted within the time window after imlifidase treatment received a kidney from a deceased donor and 7 (15%) from a living donor, Table SIII.4.

39 transplanted patients (85%) had any crossmatch positivity to the donor before the imlifidase treatment. 41 transplanted patients (89%) were highly sensitized, i.e. had a cPRA of ≥80%, of whom 8 patients (17%) had a cPRA of 80%-94.9% and 33 patients (72%) had a cPRA of ≥95%.

25 of the 46 transplanted patients (54%) belong to a group of patients who were highly unlikely to be transplanted without imlifidase. These patients all fulfil the following 3 criteria:

- Deceased donor (without any available suitable live donor)
- Crossmatch-positive to the available deceased-donor kidney
- cPRA of ≥95%

Table SIII.4: Summary of baseline characteristics (donor status, crossmatch positivity and cPRA), Safety set; all transplanted subjects

Baseline characteristics		**Transplanted patients N=46 n (%)**
Donor status	Deceased	39 (84.8)
	Living	7 (15.2)
Any crossmatch positivity	Yes	39 (84.8)
cPRA (%)[a] (MFI cut-off: 3000) or historical peak PRA	<80%	5 (10.9)
	≥80%	41 (89.1)
	80%-94.9%	8 (17.4)
	≥ 95%	33 (71.7)
Deceased donor, any crossmatch positivity and cPRA ≥ 80%		30 (65.2)
Deceased donor, any crossmatch positivity and cPRA ≥ 95%		25 (54.3)

[a] As in Organ Procurement and Transplantation Network (OPTN), the highest recorded cPRA is used

Long-term outcomes

37 of the 46 patients transplanted after imlifidase administration in studies 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 or 15-HMedIdeS-06 were included in the long-term follow-up study 17-HMedIdeS-14.

The long-term follow-up of patients showed an overall patient survival of 92% and a death-censored graft survival of 91% at 5-years after transplantation, Tables SIII.5 and SIII.6.

No adverse events or serious adverse events were reported during the follow-up study, and no safety concern related to the treatment with imlifidase has been identified.

Table SIII.5: Overall patient survival by time period

Time point	At Risk [a]	Event [b]	Censored [c]	Survival Estimates (95% CI)
1 year	35	2	0	0.95 (0.80, 0.99)
2 years	34	3	0	0.92 (0.77, 0.97)
3 years	32	3	2	0.92 (0.77, 0.97)
5 years	18	3	16[d]	0.92 (0.77, 0.97)

[a] Patients being at risk for event at the time point, i.e. not experiencing event or censored up to the time point.
[b] Patients having event up to the time point.
[c] Patients being censored up to the time point.
[d] 12 patients attended their 5-year visit (visit window ±6 months) before the actual 5-year timepoint
Actual timepoints presented.

Table SIII.6: Graft survival (censored for death) by time period

Time point	At Risk [a]	Event [b]	Censored [c]	Survival Estimates (95% CI)
1 year	35	0	2	1.00
2 years	34	0	3	1.00
3 years	31	2	4	0.94 (0.78, 0.98)
5 years	18	3	16[d]	0.91 (0.75, 0.97)

[a] Patients being at risk for event at the time point, i.e. not experiencing event or censored up to the time point.
[b] Patients having event up to the time point.
[c] Patients being censored up to the time point.
[d] 12 patients attended their 5-year visit (visit window ±6 months) before the actual 5-year timepoint
Censored events included death with a functioning graft, withdrawal from trial without graft loss, and end of trial without graft loss. Actual timepoints presented.

Part II: Module SIV – Population not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Age <18 years

Reason for exclusion: No children were to be included in the clinical studies until sufficient data on efficacy and safety had been collected in adults.

Is it considered to be included as missing information?: No

Rationale: Children not included in the applied indication.

Age >70 years

Reason for exclusion: At some centres, no patients aged above 70 years are transplanted because of higher morbidity and mortality risks associated with advanced age. This is a commonly used exclusion criterion in clinical studies within the kidney transplantation field (Blosser et al. 2011). Three elderly patients above 65 years have been treated with imlifidase, the oldest being 73 years.

Is it considered to be included as missing information?: No

Rationale: There are no indications that the safety profile of imlifidase *per se* is different in elderly patients compared to that of the general target population.

Pregnancy and lactation

Reason for exclusion: There are no data from use of imlifidase in pregnant women since pregnancy is a contraindication to kidney transplantation in general. Studies in rabbits do not indicate direct or indirect harmful effects with respect to embryonic/foetal development.

The potential risk to embryonic/foetal development is unknown. It is unknown whether imlifidase is excreted in human milk and a risk to newborns/infants cannot be excluded.

Is it considered to be included as missing information?: No

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	 • 2* of 54 patients with CKD (3.7%) had hepatic impairment reported at baseline. • All 54 patients with CKD had severe renal impairment (CKD Stage 5 / ESRD). • 48 of 54 patients with CKD (88.9%) had cardiovascular impairment at baseline. • All patients received an immunosuppressive regimen as part of the standard of care. • All 54 patients with CKD had severe renal impairment.
Population with relevant different ethnic origin	43 patients (79.6%) were 'White', 4 (7.4%) were 'Black or African American' and 7 (13.0%) were of 'Other' origin.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	Not applicable.

*Including 1 patient with 'Hepatic cyst' (multiple benign hepatic cysts in combination with polycystic kidney disease) and 1 patient with 'Lupus hepatitis, none of whom met the criteria for Hy's law (i.e. they did not have ≥ 3 x upper level of normal (ULN) of the liver enzymes ALT or AST concomitantly with serum total bilirubin of > 2 x ULN, without initial findings of cholestasis (elevated serum ALP)).

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The number of patients exposed post-authorisation is based on the information on individual delivery of Idefirix.

SV.1.2 Exposure

Idefirix was first authorised on 25 August 2020 through centralised procedure in the European Union (EU) and this date was established as the International Birth Date and the European Union Reference Date.

Since the 25 August 2020 until the DLP of this RMP, 16 patients have been exposed to Idefirix according to labelled therapeutic indication. 16 patients have been exposed to Idefirix for off-label use during this period.

Available information on the use of Idefirix in special populations is limited from the data collected through post-marketing reporting and literature. Since the 25 August 2020 until the DLP of this RMP, 1 case report of Idefirix use in the paediatric population and 4 cases of Idefirix use in the elderly population have been retrieved.

Table SV.1: Exposure table by indication and region

Indication	Region		
	All	EU country	Non-EU country
Overall	32	29	3
Labelled therapeutic indication*	16	16	0
Off-label use	16	13	3

* Idefirix is indicated for desensitisation treatment of highly sensitized adult kidney transplant patients with a 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.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the mode of action, the pharmacological properties, and the administration of a single dose supervised by a specialist physician experienced in the management of renal transplant patients, imlifidase is unlikely to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes. In addition, imlifidase should be restricted to hospital use and is administered as a single dose.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP: Risk not observed in the clinical studies and not expected at recommended dosing regimen:

Development of anti-drug antibodies

Antibodies against bacterial proteins are very common in the human population and originate from previous bacterial infections (Kanclerski et al. 1996). Most individuals have antibodies against imlifidase, i.e. anti-drug antibodies (ADAs), due to previous exposure to *S. pyogenes*.

Imlifidase is intended to be administered as a single infusion prior to deceased-donor kidney transplantation with the possibility of repeating the administration within 24 hours if the first dose is insufficient for crossmatch conversion. The potential influence of ADAs on the efficacy and safety of a second imlifidase dose given within 24 hours of the first dose is expected to be negligible, since the production of ADAs in response to the first dose has not yet started to develop.

A transient increase in anti-imlifidase IgG antibodies was seen in most patients at 1-4 weeks after administration of imlifidase in the clinical studies, without any identified safety impact. No adverse events were reported to be associated with ADAs in the clinical studies and are not expected at recommended dosing regimen.

Based on available data, the potential risk could be considered to be acceptable in relation to the severity and unmet need of the indication treated.

Preventability: Information about immunogenicity is included as a special warning and precaution in the current SmPC section 4.4.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP: Risks with minimal clinical impact on patients in relation to the severity of the indication treated:

Severe or serious myalgia

In the pre-defined analysis of at least possibly related AEs across all clinical studies within this programme, 1 of the 54 patients with CKD (1.9%) exposed to imlifidase experienced 'Severe or serious myalgia'. This patient had extensive follow-up including muscle biopsy, electromyography (EMG) and muscle-related biomarkers, which showed no abnormalities. Furthermore, no patients have developed rhabdomyolysis.

Myalgia has also been reported during treatment with other biologics such as IVIg and rituximab (Orbach et al. 2005) (SmPC for MabThera [rituximab]).

Myalgia is considered to have minimal clinical impact on patients in relation to the severity of the indication treated, and since the patient with the severe and serious myalgia had no objective findings of muscle damage and there were no subsequent cases of severe or serious myalgias reported, myalgia is not considered an important risk of imlifidase treatment.

Preventability: Information about severe and serious myalgia is included in the current SmPC section 4.8.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP: Risk not observed in the clinical studies within current indication:

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 can develop within 1-2 weeks. Symptoms may be fever, rash, joint pain, and lymphadenopathy. Complications may include vasculitis, neuropathy, acute renal failure, glomerulonephritis (rare), anaphylaxis, or shock.

Serum sickness has not been observed in nonclinical toxicology studies with imlifidase.

In clinical studies with imlifidase, no patients with CKD (N=54) experienced serum sickness.

Serum sickness was reported in a clinical study evaluating imlifidase within another indication, thrombotic thrombocytopenic purpura (TTP). In that study, 2 of 2 subjects developed serious serum

sickness on Day 6, which was assessed as related to imlifidase. Both cases resolved but due to the seriousness of these events, the clinical programme within that indication was terminated. Notably, at the time of these events, there were only very low levels of imlifidase left in the circulation, i.e. not enough to form immune complexes with anti-drug antibodies.

However, although serum sickness has not been observed after treatment with imlifidase in patients with CKD, co-morbidity with TTP has been included as a contraindication in Section 4.3 of the current SmPC as patients with TTP may be at risk of developing serum sickness.

Serum sickness may be a class effect of some biologics, possibly with individuals with certain concomitant diseases, such as TTP, being more vulnerable (Sandhu et al. 2012; Davies et al. 1990; Karmacharya et al. 2015; Le Guenno et al. 2011). Published cases of serum sickness have resolved rapidly upon treatment with corticosteroids (Karmacharya et al. 2015; Le Guenno et al. 2011)

In summary, a risk of serum sickness cannot be ruled out although not observed in patients with CKD. The risk is considered to be acceptable in relation to the severity and unmet need of the indication treated.

Preventability: In the current SmPC section 4.3, TTP is included as a contraindication, since patients with this blood disorder may be at risk of developing serum sick.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risk: Severe or serious infections

Benefit-risk impact: In this patient population, undergoing surgery, being hospitalized and receiving immunosuppressive treatment, reduced IgG levels is a risk factor for severe or serious infections. The most common infections in patients with hypogammaglobulinemia are respiratory tract infections (Oksenhendler et al. 2008). Overall, compared with the standard of care after kidney transplantation in general, an oral antibiotic agent covering bacteria causing respiratory tract infections was added in the clinical studies with imlifidase, to reduce the risk of such infections. When following this regimen, the pattern of severe infections in patients transplanted after imlifidase treatment was similar to that observed in other kidney-transplanted patients. No specific type or site of infection was identified to be more common in patients transplanted after imlifidase treatment than in other kidney-transplanted patients.

The risk of severe and serious infections can be considered to be acceptable in relation to the severity and unmet need of the indication treated, and the availability of prophylactic antibiotics to reduce the risk of infections.

Important identified risk: Infusion-related reactions

Benefit-risk impact: Infusion reactions from IV administration with a severe or serious outcome may occur, if not prevented or managed appropriately. The risk of infusion-related reactions can be considered to be acceptable in relation to the severity and unmet need of the indication treated, and pre-treatment with antihistamines and glucocorticoids, and close monitoring during the infusion to minimise the risk of infusion-related reactions.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable, no change in the list of safety concerns in the updated RMP v2.0 from RMP v1.0 submitted for imlifidase.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Severe or serious infections:

MedDRA SOC: Infections and infestations

Potential mechanisms: Based on the mode-of-action of imlifidase, which is to temporarily reduce the level of IgG, an increased risk of infections cannot be ruled out when IgG levels are compromised, especially in a population that already receives an immunosuppressive regimen as part of the standard of care. The most common infections in patients with hypogammaglobulinemia are respiratory tract infections (Oksenhendler et al. 2008). IgG subclass deficiency is a risk factor for infections caused by encapsulated bacteria such as *H. influenzae* and pneumococci (Martinot et al. 2014). It can be expected that IgG levels start to return after 1-2 weeks and continue to increase over the next weeks or return if IVIg is administered (in many cases in the clinical studies, IVIg was administered approximately 1-2 weeks after transplantation in patients treated with imlifidase).

Evidence source(s) and strength of evidence: Infections are very common in transplanted patients receiving immunosuppression. Among 60,702 kidney transplant recipients in the US Renal Data System registry records for Medicare-insured kidney transplant recipients in 2000–2011, 45% experienced at least 1 infection over 1 year (Naik et al. 2016). The overall incidences of urinary tract infection, sepsis and pneumonia in patients transplanted after imlifidase treatment were similar to those reported for kidney-transplanted patients in the Naik study:

- Urinary tract infection was reported in 33% of patients transplanted after imlifidase treatment vs 32% in the Naik study (Naik et al. 2016).
- Sepsis, urosepsis or bacteraemia was reported in 13% of patients transplanted after imlifidase treatment vs 12% in the Naik study (Naik et al. 2016).
- Pneumonia was reported in 9% of patients transplanted after imlifidase treatment vs 13.0% in the Naik study (Naik et al. 2016).

According to a published European retrospective study with 957 kidney-transplanted patients, sepsis was frequently reported after kidney transplantation (12% of patients) and was associated with decreased patient survival (3% of patients died due to sepsis) (Schachtner et al. 2017). Pneumonia was found to be a predictive factor of sepsis-associated mortality (Schachtner et al. 2017).

In clinical studies with imlifidase, 9 of 54 patients (16.7%) with CKD experienced any severe or serious infection assessed as at least possibly related to imlifidase. No fatal infections occurred in the clinical studies.

Characterisation of the risk:

A pre-specified analysis of infections was performed, which included all serious and all severe AEs of any preferred term within the system organ class (SOC) 'Infections and infestations' over the full study duration in all completed clinical studies within the clinical programme.

Nine of the 74 subjects (12%) exposed to imlifidase had any at least possibly related severe or serious infection; 7 of 46 transplanted patients with CKD (15%), 2 of 8 non-transplanted patients (25%) and 0 of the 35 healthy volunteers (0%). Preferred terms of at least possibly related severe or serious infection occurring in more than 1 subject included 'pneumonia' (3 patients) and 'sepsis' (2 patients).

Overall, these data support that the underlying disease contributes to the development of infections. When looking at all severe or serious infections, irrespective of relationship to imlifidase, the frequency of such AEs was higher in transplanted patients (43%) than in non-transplanted patients (25%) suggesting that not only the underlying disease but also the immunosuppressive treatment and the transplantation itself contributed to the development of infections.

Risk factors and risk groups: No firm conclusions can be drawn with regard to subgroups due to small numbers of patients per subgroup.

Preventability: To mitigate the risk of infections, oral prophylactic antibiotics covering respiratory infections should be added to the standard of care for 4 weeks. Ongoing serious infections is a contraindication.

Impact on the risk-benefit balance of the product: The risk of severe and serious infections can be considered to be acceptable in relation to the severity and unmet need of the indication treated. To mitigate the risk of infections, oral prophylactic antibiotics covering respiratory infections should be added to the standard of care for 4 weeks. Appropriate treatment should be given if any infection occurs. Ongoing serious infections is a contraindication.

Public health impact: None.

Important identified risk: Infusion-related reactions:

MedDRA SMQ: Anaphylactic reaction

MedDRA PT: Infusion-related reactions

Potential mechanisms: Two types of infusion reactions are described in the literature, true IgE-mediated clinical hypersensitivity reactions, and non-antibody-mediated anaphylactoid reactions (Vogel 2010; Asselin 2016). IgG antibodies against imlifidase, i.e. anti-drug antibodies (ADAs), are common since most individuals have previously been exposed to *S. pyogenes*. Anti-imlifidase IgE antibodies have not been detected in any subjects in the clinical studies. Infusion reactions are therefore most likely non-antigen-specific, the mechanism of which is not fully known, and may result from e.g. cytokine release, activation of the complement system, activation of the coagulation system, or other causes (Asselin 2016).

Evidence source(s) and strength of evidence: As for other biologic agents administered IV, infusion reactions may occur (Choquette et al. 2015). Not only IV treatment with monoclonal antibodies and other proteins, but also vehicles, have been associated with infusion reactions. It is presumed to be secondary to non-immunologic histamine-release reactions, though the exact mechanism is not known. Mild-to-moderate reactions are characterized by flushing, rash, fever, rigors, chills, dyspnoea, and mild hypotension. Severe reactions are associated with bronchospasm, hypotension, cardiac dysfunction, anaphylaxis, and other symptoms requiring treatment. To mitigate the risk of infusion-related reactions, all subjects should receive glucocorticoid and antihistamine treatment prior to dosing.

In clinical studies with imlifidase, 3 of 54 patients (6%) with CKD experienced any infusion-related reaction assessed as at least possibly related to imlifidase. In 2 of these patients, infusion of imlifidase could be resumed within less than half an hour. No fatal infusion-related reactions occurred in the clinical studies. The overall frequency as well as the frequency of serious infusion-related reactions are in the low range of reported frequencies for biologics (Baldo 2013; LaCasce et al. 2018; Song et al. 2012).

Characterisation of the risk: A pre-specified analysis of potential 'Infusion-related reactions' occurring from start of administration of imlifidase until transplantation (or within 48 hours of administration of

imlifidase in healthy volunteers and non-transplanted patients with CKD) was performed. These events were defined by an algorithmic approach based on the SMQ 'Anaphylactic reaction'. In addition, the preferred term 'Infusion-related reaction' was included consistently with a published strategy for categorization of infusion-related reactions (Siemers et al. 2016).

Based on this algorithmic approach, 1 of 35 healthy volunteers receiving imlifidase (3%), 1 of 14 healthy volunteers receiving placebo (7%) and 3 of 54 patients (6%) with CKD (2 of 46 patients transplanted within the time window of imlifidase) had at least one potential infusion-related reaction assessed as at least possibly related to imlifidase. No infusion-related reactions were of severe intensity, but 1 infusion-related reaction of moderate intensity was serious (resolved after 90 minutes) and resulted in discontinuation of the dosing and the patient not being transplanted.

The occurrence of 'Infusion-related reactions' also in the placebo group indicates that the infusion itself may have contributed to these events. At least possibly related AEs categorised as 'Infusion-Related Reaction' occurring in more than 1 subject included the preferred terms 'Infusion Related Reaction' reported by 3 subjects and 'Flushing' reported by 2 subjects.

Risk factors and risk groups: No firm conclusions can be drawn with regard to subgroups due to small numbers of patients per subgroup.

Preventability: To mitigate the risk of infusion-related reactions, patients should receive glucocorticoid and antihistamine treatment prior to dosing and should be closely monitored during the infusion.

Impact on the risk-benefit balance of the product: The risk of infusion-related reactions can be considered to be acceptable in relation to the severity and unmet need of the indication treated. To mitigate the risk of infusion-related reactions, patients should receive glucocorticoid and antihistamine treatment prior to dosing and should be closely monitored during the infusions.

Public health impact: None.

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

A summary of the safety concerns identified in previous Module SVII of Part II is provided in Table SVIII.1.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Severe or serious infection Infusion-related reactions
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are planned.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study name Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Category 1				
20-HMedIdeS-20 PAES 5-year-extension study	Evaluate long-term graft survival in patients who have undergone kidney transplantation after imlifidase administration and in patients in the non-comparative concurrent reference cohort.	Additional long-term effectiveness and safety	Synopsis submission Synopsis submitted on 24-Nov-2020 Supplementary Information to Synopsis submitted on 16-Mar-2021 Endorsed by CHMP 24-Jun-2021	30-11-2020
			Study report	31-12-2030
Category 2				
20-HMedIdeS-19 PAES to evaluate 1-year graft survival, kidney function and safety after imlifidase Planned start Q2 2022	1-year overall graft survival in subjects following pre-treatment with imlifidase in kidney transplant patients with positive crossmatch. 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	Additional long-term effectiveness and safety	Protocol submission Protocol submitted as standalone PAM on 17-Dec-2020 Supplementary Information to Protocol submitted on 06-Apr-2021 Endorsed by CHMP 24-Jun-2021	31-12-2020

	transplanted patients (any grade of sensitization) 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, safety profile (including serious and severe infections, and infusion-related reactions), QoL.		Study report	31-12-2025

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Infections	Routine risk communication: Ongoing serious infections is included as a contraindication in the current SmPC, section 4.3. Recommendation that Idefirix should be administered in combination with oral prophylactic antibiotics, covering respiratory infections, to reduce the risk of infections is included in the current SmPC section 4.2., 4.4 and 4.8. Information about infections in the PL section 2 and 4.
Infusion–related reactions	Routine risk communication: Recommendation that Idefirix treatment should be supervised by specialist physicians experienced in the management of immunosuppressive therapy and of renal transplant patients is included in the current SmPC section 4.2 and PL section 3. Recommendation that Idefirix should be administered in combination with corticosteroids and antihistamines to reduce the risk of infusion-related reactions is included in the current SmPC section 4.2 and 4.8. Recommendation that if any serious allergic or anaphylactic reaction occurs, Idefirix therapy should be discontinued immediately, and appropriate therapy initiated is included in the current SmPC section 4.4. Information

	about allergic reactions and infusion-related reactions in the PL section 2 and 4.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are considered sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infections	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 4.8. PL section 2 and 4.	Routine pharmacovigilance activities. Additional pharmacovigilance activities: 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). Final study report 31 December 2025 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. Final study report 31 December 2030.
Infusion–related reactions	Routine risk communication: SmPC section 4.2., 4.4 and 4.8. PL section 2, 3 and 4.	Routine pharmacovigilance activities. Additional pharmacovigilance activities: 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). Final study report 31 December 2025.

Part VI: Summary of the risk management plan

Summary of risk management plan for Idefirix (imlifidase)

This is a summary of the risk management plan (RMP) for Idefirix. The RMP details important risks of Idefirix, how these risks can be minimised, and how more information will be obtained about Idefirix's risks and uncertainties (missing information).

Idefirix's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Idefirix should be used.

This summary of the RMP for Idefirix should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Idefirix's RMP.

I. The medicine and what it is used for

Idefirix is authorised for desensitization treatment of highly sensitized 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 prioritization programmes for highly sensitized patients.

Idefirix contains imlifidase as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Idefirix’s benefits can be found in Idefirix’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Idefirix, together with measures to minimise such risks and the proposed studies for learning more about Idefirix's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Idefirix is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Idefirix are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Idefirix. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Severe or serious infection Infusion-related reactions
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Severe and serious infection	
Evidence for linking the risk to the medicine	Idefirix cleaves a type of antibodies called immunoglobulin G (IgG) to prevent IgG from destroying the kidney transplant. In the period when IgGs are cleaved, there may be a higher risk of some infections. Infections are very common in transplanted patients receiving immunosuppression. In a large published study in kidney-transplanted patients not treated with Idefirix, about half of the patients had at least 1 infection during the first year after transplantation. About one third of the patients had urinary tract infection, 13% had pneumonia, and 12% had sepsis (a serious infection that causes the immune system to attack the body). In clinical studies with Idefirix, 9 of 54 patients (16.7%) with chronic kidney disease (CKD), whereof 7 of 46 kidney-transplanted patients (15%), had any severe or serious infection assessed as at least possibly related to Idefirix. No patients died from infections or from any other cause in the clinical studies with Idefirix. To minimise the risk of infections, all patients should receive treatment with antibiotics.

Risk factors and risk groups	No firm conclusions can be drawn regarding subgroups due to small numbers of patients per subgroup.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2., 4.3, 4.4 and 4.8. PL section 2 and 4.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 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). Study 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. See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	As for other biologic treatments administered intravenously (IV), infusion reactions may occur. Not only IV treatment with monoclonal antibodies and other proteins, but also IV infusion without active drug, has been associated with infusion reactions, though the exact mechanism is not known. Mild-to-moderate reactions are characterized by flushing, rash, fever, rigors, chills, shortness of breath, and low blood pressure. Severe reactions are associated with bronchospasms (narrowing of the airways), low blood pressure, heart dysfunction, severe allergic reaction, and other symptoms requiring treatment. In clinical studies with Idefirix, 3 of 54 patients (5.6%) with CKD had any infusion-related reaction assessed as related to Idefirix (whereof 2 patients were kidney-transplanted). In 2 of the 3 patients, infusion of Idefirix could be restarted within less than half an hour. No patients died from infusion-related reactions in the clinical studies with Idefirix. To minimize the risk of infusion-related reactions, all patients should receive glucocorticoid and antihistamine treatment before dosing.
Risk factors and risk groups	No firm conclusions can be drawn with regard to subgroups due to small numbers of patients per subgroup.
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.2., 4.4 and 4.8. PL section 2, 3 and 4.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 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). See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

This section will be updated according to the recommendation and decisions by PRAC and CHMP during the procedure, as applicable.

The following studies are conditions of the marketing authorisation:

Study 20-HMedIdeS-19: Post-approval efficacy study (PAES)

Purpose of the study: To assess 1-year overall graft survival rate in highly sensitized kidney transplant patients with positive crossmatch against a deceased donor and pre-treated with imlifidase. The study will include two non-comparative reference cohorts for descriptive purpose; one registry-based with kidney-transplanted patients and a second concurrent reference cohort with transplanted patients (any grade of sensitization) not enrolled to the imlifidase treatment. The study will also evaluate kidney function, patient survival, frequency of crossmatch conversion, safety profile (including serious and severe infections, and infusion-related reactions), and quality of life.

Study 20-HMedIdeS-20: Post-approval efficacy study (PAES) long-term follow-up study

Purpose of the study: 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 and in patients in the non-comparative concurrent reference cohort.

II.C.2 Other studies in post-authorisation development plan

This section will be updated according to the recommendation and decisions by PRAC and CHMP during the procedure, as applicable

There are no studies required for Idefirix.

Part VII: Annexes

Table of contents

[redacted]

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

[redacted]

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

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