Drugs (2020) 80:1859–1864
https://doi.org/10.1007/s40265-020-01418-5

ADISINSIGHT REPORT

Imlifidase: First Approval

Zaina T. Al-Salama[1]

Published online: 15 October 2020
© Springer Nature Switzerland AG 2020

Abstract
Imlifidase (Idefirix™), a cysteine protease derived from the immunoglobulin G (IgG)-degrading enzyme of *Streptococcus (S.) pyogenes* is being developed by Hansa Biopharma AB for treatment of transplant rejection and rare IgG-mediated autoimmune conditions. In August 2020, intravenous imlifidase received its first global approval in the EU for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor. Imlifidase is currently undergoing clinical evaluation for the prevention of kidney transplant rejection in the USA, Australia, France and Austria, and clinical development is underway for anti-glomerular basement membrane disease, and for Guillain–Barre syndrome in France, the UK and the Netherlands. This article summarizes the milestones in the development of imlifidase leading to this first approval for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor.

Imlifidase (Idefirix™): Key Points

A cysteine protease derived from the IgG-degrading enzyme of *S. pyogenes* is being developed by Hansa Biopharma AB for treatment of transplant rejection and rare IgG-mediated autoimmune conditions

Received conditional approval on 26 August 2020 in the EU

Approved for use in the EU for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor

1 Introduction

Chronic kidney disease (CKD) is a long-term, irreversible and progressive disease, and kidney transplantation is considered the treatment of choice in end-stage renal disease (ESRD) [1]. Previous exposure to human leukocyte antigen (HLA) [e.g. because of pregnancy, blood transfusion, organ transplant] causes sensitization, where patients carry antibodies to HLA; high levels of anti-HLA antibodies in highly sensitized patients is a major cause of antibody-mediated rejection (AMR) and poor graft survival [2]. Antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) are the main pathways involved in AMR.

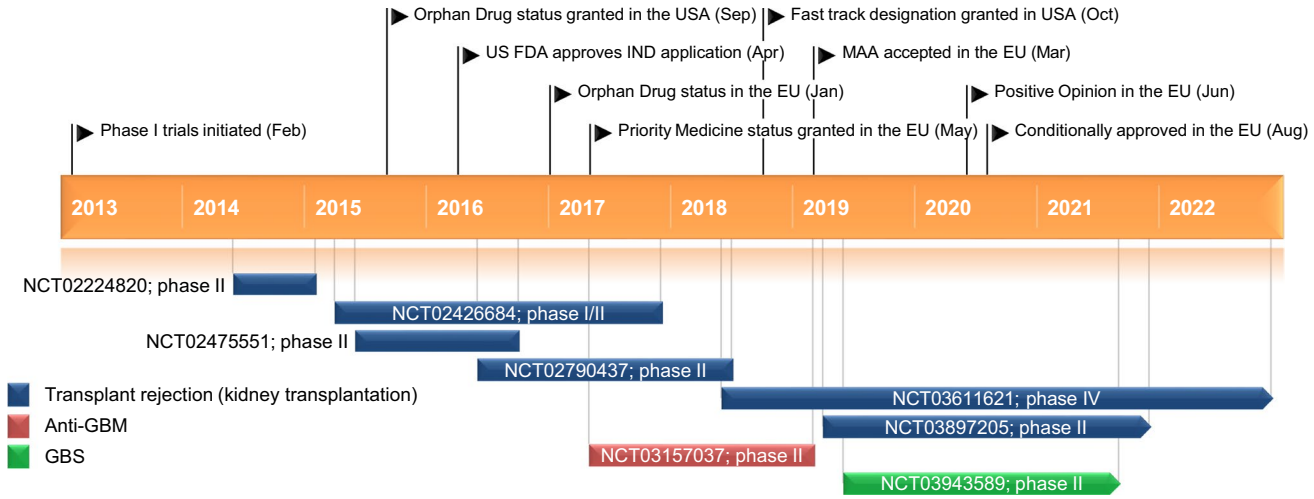
HLA sensitized patients express multiple alloantibodies that often result in crossmatch positivity due to the presence of donor-specific antibodies (DSAs) [3]. Because of the increased risk of AMR in highly sensitized patients, rates of transplantation in this patient population remain low; these patients remain on long-term dialysis, an option associated with complications, increased morbidity and mortality, poor quality of life and a high cost [1]. Current protocols are often associated with incomplete removal of DSAs, rebound antibody production, and an increased risk of acute and chronic AMR; these are the main causes of early graft loss and return to dialysis [1]. Therefore, an unmet medical need exists to desensitize highly sensitized patients, and convert

Enhanced material for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.12981116.

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through preclinical and clinical studies to market launch and beyond.

✉ Zaina T. Al-Salama
dru@adis.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand



Key milestones in the development of imlifidase, focusing on its use in desensitization treatment of highly sensitized adult kidney transplant patients. *GBM* glomerular basement membrane, *GBS* Guillain–Barre syndrome, *IND* Investigational New Drug, *MAA* Marketing Authorization Application, *US FDA* Food and Drug Administration

a positive crossmatch into a negative one to allow kidney transplantation.

Imlifidase (Idefirix™) is a cysteine protease derived from the immunoglobulin G (IgG)-degrading enzyme of *Streptococcus (S.) pyogenes* being developed by Hansa Biopharma AB (known as Hansa Medical AB prior to December 2018) for transplant rejection and rare IgG-mediated autoimmune conditions [4]. Based on positive results from four phase II trials, imlifidase received conditional approval in the EU on 26 August 2020 for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor [4, 5]. The use of imlifidase should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritization programmes for highly sensitized patients [5]. Imlifidase is available as a powder for concentrate for solution for infusion (11 mg). The recommended dosage is 0.25 mg/kg administered as a single dose over 15 min preferably within 24 h of transplantation; although one dose is adequate for crossmatch conversion in the majority of patients, a second dose can be administered within 24 h after the first dose if needed. After imlifidase treatment, confirmation of crossmatch conversion from positive to negative should be performed before transplantation. Imlifidase is contraindicated in patients with an ongoing serious infection or thrombotic thrombocytopenic purpura (due to the risk of developing serum sickness) [5].

Imlifidase has orphan drug designation for anti-glomerular basement membrane (GBM) disease in the EU and the USA, Guillain–Barre syndrome (GBS) in the USA, and the prevention of antibody-mediated organ rejection in solid organ transplant patients in the USA, and for the prevention of graft rejection following solid organ transplantation in the EU. Imlifidase is currently undergoing clinical evaluation for the prevention of kidney transplant rejection in the USA, Australia, France and Austria, and clinical development is underway for anti-GBM disease, and for GBS in France, the UK and the Netherlands. Clinical evaluation of imlifidase for rheumatoid arthritis, streptococcal infections and thrombotic thrombocytopenic purpura has been discontinued.

1.1 Company Agreements

In July 2020, Hansa Biopharma AB entered into an exclusive licensing agreement with Sarepta Therapeutics Inc., to develop and promote imlifidase as a pre-treatment to enable Sarepta's gene therapy treatment in patients with Duchenne muscular dystrophy and limb-girdle muscular dystrophy with pre-existing neutralizing antibodies to adeno-associated virus (AAV), the technology for Sarepta's gene therapy products. Under the terms of the agreement, Hansa is entitled to an upfront payment, is eligible to receive development, regulatory and sales milestone payments, as well as royalties on any gene therapy sales enabled through pre-treatment with imlifidase in patients with neutralizing antibodies [6]. In February 2015, Hansa Medical AB initiated a co-operation with Cedars-Sinai Medical Center's Comprehensive Transplant Center and a US transplantation expert, to assist in the development of imlifidase in transplantation [7].

1.2 Patent Information

In July 2016, Hansa Medical AB filed for a patent protection for combination of imlifidase with approved anti-cancer therapies [8]. In February 2015, Hansa announced that it was

developing and submitting a patent application for a second generation imlifidase molecule that allows repeated dosage, and which could potentially include chronic autoimmune disease as another therapeutic indication [9]. In March 2012, Hansa was granted a US patent (patent number 8 133 483) and a European patent (1 901 773), covering the medical use of imlifidase for the prevention and treatment of IgG-mediated indications, including transplant rejection and autoimmune diseases [10].

2 Scientific Summary

2.1 Pharmacodynamics

Imlifidase is a streptococcal protease with a unique degree of specificity for IgG (its only substrate) and cleaves IgG in two steps; the first reaction is cleavage of one of the two heavy chains to generate a single cleaved IgG molecule, followed by a second reaction to generate one $F(ab')_2$ and one Fc fragment; this results in elimination of Fc-dependent effector functions including CDC and ADCC [11]. The cleavage of all IgG by imlifidase reduces the levels of DSAs, and enables transplantation [5].

In vitro, imlifidase demonstrated dose-dependent inhibition of anti-HLA antibody-mediated natural killer cell activation and antibody-dependent cell-mediated cytotoxicity; the maximum therapeutic concentration of imlifidase (10 µg/ml) was associated with the greatest inhibition [2]. In the sera of treated patients, imlifidase treatment significantly decreased the levels of anti-HLA antibodies and significantly inhibited the capacity of anti-HLA antibody-mediated natural killer cell and natural killer T cell activation, post treatment.

In allosensitized recipient mice, enzymatic inactivation of DSAs using imlifidase in combination with endoglycosidase of *S. pyogenes* improved the survival of donor bone marrow cells and in combination with other desensitization strategies, allowed allogenic bone marrow engraftment [12].

In a mouse model of anti-GBM disease (injected with subnephritogenic doses of rabbit anti-mouse GBM, followed a week later by injection of monoclonal mouse anti-rabbit IgG antibodies), imlifidase degraded IgG bound to the GBM and prevented renal damage [13]. Imlifidase effectively removed the Fc fragments of the rabbit IgG and significantly reduced the deposition of the complement components C3 and C1q; the latter effect diminished the recruitment of leukocytes to the glomeruli. Imlifidase also prevented albuminuria in these animal models [13].

Imlifidase administration was associated with a decrease in anti-AAV antibodies and enabled efficient liver gene transfer in mice passively immunized with intravenous (IV) IgG, and enhanced liver transduction in nonhuman primates when administered before AAV vector infusion (including vector re-administration setting) [14]. In vitro, imlifidase reduced levels of anti-AAV antibodies in human plasma samples (including plasma from prospective gene therapy trial participants).

In a randomized, double-blind, dose-escalation phase I trial (NCT01802697; study 01), imlifidase (0.01–0.24 mg/kg) administered to healthy male volunteers cleaved the plasma IgG pool into single cleaved IgG within minutes of dosing; low plateau levels of IgG < 5% of the original signal were detected in blood 2–6 h after imlifidase administration and remained low until newly synthesized intact IgG appeared in plasma after 1–2 weeks [11]. The phagocytic capacity of IgG/IgG fragments was significantly reduced 2 h after imlifidase (0.24 mg/kg) administration, and remained low for at least 1 week [11].

In a single-centre, open-label, ascending-dose (0.12 mg/kg × 2, 0.25 mg/kg × 1 or 0.25 mg/kg × 2) phase II trial (NCT02224820; study 02) in highly sensitized patients with CKD ($n = 8$), imlifidase demonstrated IgG degradation in all patients, with < 1% of plasma IgG remaining within 48 h and remaining low for up to 1 week [15]. Imlifidase reduced mean fluorescence intensity (MFI) values of HLA class I and II in all patients and eliminated C1q binding to anti-HLA antibodies; IgG-type B cell receptors on CD19+ memory B cells were also cleaved by imlifidase [15].

Given that imlifidase specifically cleaves IgG, medicinal products based on human or rabbit IgG [e.g. rituximab, IV immunoglobulin (IVIg)] may be inactivated if coadministered with imlifidase; appropriate time intervals between administration of imlifidase and these products should be applied [5]. IVIg may contain antibodies against imlifidase; therefore, its half-life of 3–4 weeks should be considered before administration of imlifidase in these patients [5].

2.2 Pharmacokinetics

The pharmacokinetic properties of imlifidase were comparable in healthy subjects and patients with ESRD [5]. Following single 15-min IV doses of imlifidase (0.12–0.50 mg/kg), exposure increased in a dose-proportional manner. Imlifidase maximum plasma concentrations were observed at or soon after the end of infusion [5]. Elimination was characterized by an initial distribution phase with a mean half-life of 1.8 h and a slower elimination phase with a mean half-life of 89 h. During the elimination phase, the volume of distribution was 0.2 L/kg and the mean clearance was 1.8 mL/h/kg [5].

Features and properties of imlifidase	
Alternative names	HMed-IdeS; IdeS; IgG-degrading enzyme of *Streptococcus pyogenes*; IgG-endopeptidase; Mac-1; streptococcal cysteine proteinase; Idefirix™
Class	Antibacterials; antineoplastics; antirheumatics; bacterial proteins; endopeptidases; immunotherapies
Mechanism of Action	Immunoglobulin inhibitors; immunosuppressants
Route of Administration	Intravenous
Pharmacodynamics	Cleaves the heavy chains of all human IgG subclasses (but no other immunoglobulins); eliminates Fc-dependent effector functions (including complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity); reduces the level of donor specific antibodies, enabling transplantation
Pharmacokinetics	Dose-proportional exposure; elimination characterized by a distribution and an elimination phase (mean half-life of 1.8 and 89 h); volume of distribution 0.2 L/kg and mean clearance 1.8 mL/L/kg
Most frequent adverse events	Infections, sepsis, infusion site pain, infusion related reactions, increased alanine aminotransferase, increased aspartate aminotransferase, myalgia, headache and flushing
ATC codes	
WHO ATC code	L04A-A41 (imlifidase)
EphMRA ATC code	L4X (other immunosuppressants)
Chemical Formula	$C_{1575}H_{2400}N_{422}O_{477}S_6$

2.3 Therapeutic Trials

Imlifidase enabled kidney transplantation in all 10 patients in the Swedish phase II study (NCT02475551; study 03) and all 17 patients in the US phase I/II study (NCT02426684; study 04) [5], when given before kidney transplantation in highly sensitized patients to reduce or eliminate DSAs and to allow transplantation from an incompatible donor without antibody rejection [16]. DSAs were reduced in all patients who were DSA-positive at baseline in both studies, and all positive crossmatches were converted to negative after imlifidase treatment in study 03 [5]. At 6 months, 100 and 94% of transplanted patients had a functioning kidney in studies 03 and 04 and kidney function was restored to the expected range for kidney-transplanted patients with 80 and 94% of patients having an estimated glomerular filtration rate (eGFR) of > 30 mL/min/1.73 m^2 [5]. Three and two patients had AMR in the Swedish and US studies, but did not lead to graft loss in any of these patients.

Studies 03 and 04 were two independently-performed open-label transplantation studies to evaluate the efficacy and safety of imlifidase given before kidney transplantation in highly sensitized patients to reduce or eliminate DSAs and to allow transplantation from an incompatible donor without early antibody rejection, conducted in Sweden [a single dose of 0.25 ($n = 5$) or 0.5 ($n = 5$) mg/kg] and in the USA (a single dose of 0.24 mg/kg; $n = 17$) [16]. Eligible patients (aged 18–70 years) were undergoing dialysis for ESRD and were on their regional waiting list for a transplant; all patients had extensive sensitization [median calculated panel-reactive antibody (cPRA) level of 95%] and had a clinically significant sensitization history. Patients received prophylactic antibiotic agents and continued to receive standard immunosuppression; IVIg and rituximab were also administered after transplantation in the US study [16].

Imlifidase enabled all highly sensitized patients ($n = 18$) to undergo kidney transplantation resulting in good kidney function and graft survival in a multinational, single-arm, 6-month, open-label phase II trial (NCT02790437; study 06) [17, 18]. Following imlifidase infusion, a positive crossmatch was converted to a negative one in 17 patients (primary endpoint) and one patient was borderline; 25% of patients had biopsy proven AMR (effectively treated using standard of care therapy and mostly attributable to DSA rebound), and there were two graft losses due to primary nonfunction. Patient survival at the end of the study was 100% and the median eGFR was 50 mL/min/1.73 m^2 [18].

Study 06 enrolled patients who exhibited DSAs with a positive crossmatch test to their available live deceased donors, and had previously undergone desensitization unsuccessfully or in whom effective desensitization would have been highly unlikely [18]. Imlifidase was administered at a dose of 0.25 mg/kg on day 0, and a second dose could be given within 2 days of the first infusion if a negative crossmatch was not achieved [1]. At baseline, all patients had a positive crossmatch to their donor and half had an immunodominant DSA >12,000 MFI; the median cPRA was 99.6% and the mean MFI was > 2000 [18].

Results from an analysis of transplanted patients ($n = 46$) from studies 03, 04 and 06 indicate that after 6 months, 93% of these patients had a functioning graft and kidney assessments demonstrated that 87% of patients with data ($n = 32$) had a well-functioning kidney; 92% of patients in the crossmatch positive group ($n = 39$) had a functioning

graft at 6 months, with a well-functioning kidney in 88% of crossmatch positive patients with data ($n = 26$) [19]. Up to 2 years after transplantation, there were no additional graft losses and the overall graft survival was 80% (24 of 30 patients); the 2-year death censored graft survival was 89% (24 of 27 patients).

Rebound DSAs may cause AMR, with early AMR requiring intervention being more likely amongst patients who had very high levels of DSAs prior to transplantation [5]. In clinical studies, most patients had DSA rebound that peaked 7–21 days after imlifidase treatment, with 30% of patients experiencing an AMR and all of whom were successfully treated with standard of care therapy [5].

2.4 Adverse Events

Across studies 02, 03, 04 and 06 ($n = 54$; 44 and 10 patients receiving 0.25 and 0.5 mg/kg of imlifidase), all patients with CKD treated with imlifidase experienced at least one treatment-emergent adverse event (TEAE) and treatment discontinuation because of a TEAE occurred in 4% of patients; 35% of patients experienced a TEAE related to imlifidase treatment [20]. Among the TEAEs considered treatment related, the most common were infections (16.7%), [including pneumonia, urinary tract infection (6% each) and sepsis (4%)], infusion site pain, infusion related reactions, increased alanine aminotransferase, increased aspartate aminotransferase, myalgia, headache and flushing (4% each) [5].

Although laboratory abnormalities were reported in a number of patients with CKD across the four clinical studies, the overall pattern was consistent with that expected in this patient population and did no fulfil the criteria for Hy's law [20].

Severe treatment-emergent serious adverse events (SAEs) occurred in 37% of patients, and were related to imlifidase treatment in 11% of patients [20]. The most common treatment-emergent SAEs considered treatment-related in clinical studies were pneumonia (6%) and sepsis (4%) [5]. SAEs (including infections), including those considered related to treatment, were reported at a higher frequency in patients receiving a total imlifidase dosage of 0.5 mg/kg than those receiving 0.25 mg/kg [20]. There were no fatal adverse events and no deaths reported in studies 02, 03, 04 or 06 to date.

2.5 Ongoing Clinical Trials

A number of multinational clinical trials are recruiting and include a randomized, open-label, multicentre, phase II trial (NCT03897205; EudraCT 2018-000022-66), which will compare imlifidase with plasma exchange therapy in eliminating donor specific anti-HLA antibodies in the treatment of active AMR in kidney transplant patients and the prospective observational, 5 year, long-term, follow-up study (NCT03611621) of patients treated with imlifidase prior to kidney transplantation, which will include patients who have participated in the imlifidase kidney transplantation studies (studies 02, 03, 04 and 06). Also currently recruiting is an open-label, multicentre, phase II study (NCT03943589; EudraCT2018-001059-12) of imlifidase in combination with standard of care IVIg in patients with GBS. An open-label, phase II trial (NCT03157037; GOOD-IDES-01) evaluating imlifidase in patients with severe anti-GBM disease in

Key clinical trials of imlifidase

Drug(s)	Indication	Phase	Status	Location(s)	Sponsor (collaborator)	Identifier
Imlifidase	Renal transplant rejection	IV	Recruiting	Multinational	Hansa Biopharma AB	NCT03611621
Imlifidase	Renal transplant rejection	II	Completed	Sweden	Hansa Biopharma AB	NCT02224820; study 02
Imlifidase	Renal transplant rejection	II	Completed	Sweden	Hansa Biopharma AB (Uppsala University Hospital; Karolinska Institutet)	NCT02475551; study 03
Imlifidase	Renal transplant rejection	I/II	Completed	USA	Cedars-Sinai Medical Center (Hansa Biopharma AB)	NCT02426684; study 04
Imlifidase	Renal transplant rejection	II	Completed	Multinational	Hansa Biopharma AB	NCT02790437; study 06
Imlifidase, plasma exchange	Renal transplant rejection	II	Recruiting	Multinational	Hansa Biopharma AB	NCT03897205
Imlifidase	Guillain–Barre syndrome	II	Recruiting	Multinational	Hansa Biopharma AB	NCT03943589
Imlifidase	Anti-glomerular basement membrane disease	II	Ongoing	Sweden	Mårten Segelmark (Hansa Biopharma AB)	NCT03157037; GOOD-IDES-01

combination with standard of care has completed recruitment and is being analysed.

3 Current Status

Imlifidase received conditional approval on 26 August 2020 in the EU for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor [4].

Acknowledgements During the peer review process, the manufacturer of imlifidase was offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of interest Zaina T. Al-Salama is a salaried employee of Adis International Ltd/Springer Nature, is responsible for the article content and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics Approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability Not applicable.

References

1. National Institute for Health Research. Imlifidase for kidney transplantation in highly sensitised patients with chronic kidney disease (NIHR health technology briefing). 2019. http://www.io.nihr.ac.uk/wp-content/uploads/2019/07/11428-Imlifidase-for-Kidney-Transplantation-V1.0-JUL2019-NONCONF.pdf. Accessed 21 Sept 2020.
2. Ge S, Chu M, Choi J, et al. Imlifidase inhibits HLA antibody-mediated NK cell activation and antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. Transplantation. 2019. https://doi.org/10.1097/tp.0000000000003023.
3. Sethi S, Choi J, Toyoda M, et al. Desensitization: overcoming the immunologic barriers to transplantation. J Immunol Res. 2017. https://doi.org/10.1155/2017/6804678.
4. Hansa Biopharma AB. The EU Commission grants conditional approval for Idefirix™ (imlifidase) in highly sensitized kidney transplant patients in the European Union [media release]. 26 Aug 2020. http://www.hansabiopharma.com.
5. European Medicines Agency. Idefirix (imlifidase): EU summary of product characteristics. 2020. https://www.ema.europa.eu/en/documents/product-information/idefirix-epar-product-information_en.pdf. Accessed 21 Sept 2020.
6. Hansa Biopharma AB. Hansa Biopharma announces exclusive agreement with Sarepta Therapeutics to develop and promote imlifidase as pre-treatment ahead of gene therapy in select indications. [media release]. 1 Jul 2020. http://www.hansabiopharma.com.
7. Hansa Medical AB. Hansa Medical AB announces cooperation with Cedars-Sinai Medical Center's Comprehensive Transplant Center and US transplantation expert Stanley Jordan [media release]. 5 Feb 2015. http://www.hansamedical.com.
8. Hansa Medical AB. Hansa Medical acquires rights to cancer immunotherapy using antibody-modulating enzymes [media release]. 19 Jul 2016. http://www.hansamedical.com.
9. Hansa Medical AB. Hansa Medical year-end report 2014 [media release]. 13 Feb 2015. http://www.hansamedical.com.
10. Hansa Medical AB. Hansa Medical granted patents in the United States and Europe for the medical use of IdeS [media release]. 14 Mar 2012. http://www.hansamedical.com.
11. Winstedt L, Järnum S, Nordahl EA, et al. Complete removal of extracellular IgG antibodies in a randomized dose-escalation phase I study with the bacterial enzyme IdeS—a novel therapeutic opportunity. PLoS ONE. 2015;10(7):e0132011.
12. Lin J, Boon L, Bockermann R, et al. Desensitization using imlifidase and EndoS enables chimerism induction in allosensitized recipient mice. Am J Transplant. 2020;20(9):2356–65.
13. Yang R, Otten MA, Hellmark T, et al. Successful treatment of experimental glomerulonephritis with IdeS and EndoS, IgG-degrading streptococcal enzymes. Nephrol Dial Transplant. 2010;25(8):2479–86.
14. Leborgne C, Barbon E, Alexander JM, et al. IgG-cleaving endopeptidase enables in vivo gene therapy in the presence of anti-AAV neutralizing antibodies. Nat Med. 2020;26(7):1096–101.
15. Lorant T, Bengtsson M, Eich T, et al. Safety, immunogenicity, pharmacokinetics, and efficacy of degradation of anti-HLA antibodies by IdeS (imlifidase) in chronic kidney disease patients. Am J Transplant. 2018;18(11):2752–62.
16. Jordan SC, Lorant T, Choi J, et al. IgG endopeptidase in highly sensitized patients undergoing transplantation. N Engl J Med. 2017;377(5):442–53.
17. Hansa Biopharma AB. Hansa Biopharma: investor presentation [presentation]. In: Citi European Healthcare Conference. 2020.
18. Jordan SC, Legendre C, Desai N, et al. Safety and efficacy of imlifidase in highly-sensitized kidney transplant patients: results from a phase 2 study. Am J Transplant. 2019;19(Suppl 3):327–8.
19. Hansa Biopharma AB. Hansa Biopharma announces long term follow-up data that demonstrates 2-year graft survival of 89% after imlifidase treatment and transplantation [media release]. 6 Mar 2020. https://news.cision.com/hansa-biopharma-ab/r/hansa-biopharma-announces-long-term-follow-up-data-that-demonstrates-2-year-graft-survival-of-89–af,c3053754.
20. European Medicines Agency. Idefirix (imlifidase): EU assessment report. 2020. https://www.ema.europa.eu/en/documents/assessment-report/idefirix-epar-public-assessment-report_en.pdf. Accessed 21 Sept 2020.