

## HEALTH TECHNOLOGY BRIEFING JULY 2019

# Imlifidase for kidney transplantation in highly sensitised patients with chronic kidney disease

<b>NIHRIO ID</b>	11428	<b>NICE ID</b>	10193
<b>Developer/Company</b>	Hansa Biopharma AB	<b>UKPS ID</b>	Not Available

<b>Licensing and market availability plans</b>	Currently in phase II trials.
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### SUMMARY

Imlifidase is in clinical development for enabling kidney transplantation in highly sensitised patients with chronic kidney disease (CKD). CKD is a long-term irreversible condition where the kidneys do not work as well as they should. Kidney transplantation is considered to be treatment of choice for patients with end stage kidney disease. Many patients on the waiting list for organ transplantation carry antibodies to human leukocyte antigen (HLA), which is known as being 'sensitised.' Patients who are highly sensitised may find it difficult getting a donor and may not be able to receive a transplant due to increased risk of kidney rejection.

Imlifidase is made of an enzyme derived from the bacterium called *Streptococcus pyogenes*. It specifically cleaves all human subclasses of proteins called immunoglobulin IgG. This mechanism inhibits all IgG mediated immunity and prevents rejection of a transplanted kidney. If licensed, imlifidase will offer a treatment that enables kidney transplantation in highly sensitised patients with CKD.

## PROPOSED INDICATION

Desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor.<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Imlifidase (Idefix, IdeS, HMED-IdeS) is an extracellular cysteine proteinase enzyme produced by *Streptococcus pyogenes*.<sup>2-5</sup> Imlifidase efficiently cleaves IgG, including donor-specific antibodies (DSAs), into F(ab')<sub>2</sub> and Fc-fragments within a few hours.<sup>6</sup> This IgG cleaving effect eliminates antibody-dependent and complement-mediated responses creating a therapeutic window for transplantation. Imlifidase can also cleave the IgG-type B-cell receptor and compromise memory B-cell activation and thus potentially counteract allograft rejection.<sup>2,3</sup>

Imlifidase is in clinical development for the desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor.<sup>a</sup> In the phase II clinical trial (NCT02790437), patients received one dose of 0.25 mg/kg bodyweight imlifidase on study day 0. If negative crossmatch was not achieved, a second dose was given within 2 days of the first infusion.<sup>1</sup>

### INNOVATION AND/OR ADVANTAGES

For most sensitised patients, due to the breadth and strength of the antibodies, there is an extremely low likelihood of successful desensitisation using currently available institutional protocols.<sup>7,b</sup> Also, these treatments require repeated dosing for several weeks to months prior to transplantation and are almost exclusively used for living-donor kidney transplantation since deceased-donor kidney transplantations must take place within hours of donor death.<sup>c</sup> Compared to established increasing morbidity and mortality associated with staying on dialysis, enabling kidney transplantation has been proven to be also economically favourable, in addition to the improvements in quality of life for the patients.<sup>8</sup>

Company has provided the EMA with sufficient information to show that this medicine might be of significant benefit for patients at risk of graft rejection following solid organ transplantation and also provided evidence of the significant medical need for highly sensitised patients who today have extremely limited opportunity for transplantation.<sup>9-11</sup> Treatment with imlifidase allows transplantation in highly sensitised patients with CKD, within the narrow time-window available for deceased-donor graft preservation. This constitutes a novel therapeutic principle for an unmet medical need for patients who otherwise might have no hope for receiving a lifesaving transplant.<sup>6,12,13</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Imlifidase does not have Marketing Authorisation for any indication in the UK.

Imlifidase was granted EU orphan designation in January 2017 for the prevention of graft rejection following solid organ transplantation.<sup>11</sup>

<sup>a</sup> Information provided by Hansa Biopharma AB

<sup>b</sup> Information provided by Hansa Biopharma AB

<sup>c</sup> Information provided by Hansa Biopharma AB

Imlifidase was granted PRIME designation in 2017 for kidney transplantation.<sup>14</sup>

Imlifidase is in phase II clinical development for Guillain-Barré Syndrome and antibody-mediated rejection in kidney transplant patients.<sup>15</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

CKD is a long-term irreversible and typically progressive condition where the kidneys do not work as well as they should. CKD can be caused by many diseases but it is often found in patients who also have diabetes and high blood pressure.<sup>16,17</sup>

CKD is classified in five stages, according to the level of kidney damage and the ability of the kidneys to filter blood.<sup>18</sup> Patients with CKD experience weight loss or poor appetite, swollen ankles, feet and hands, shortness of breath, tiredness, blood in urine and polyuria and nocturia.<sup>19</sup>

Renal transplantation is considered to be treatment of choice for patients with end stage renal disease, however, rates of transplantation remain low among patients with high levels of preformed anti-HLA antibodies.<sup>20</sup> HLA antibodies are proteins that may be present in the patient's blood, which could interfere with the success of the transplant. If the stem cell donor is not an absolutely perfect match, HLA antibodies can attack the donated stem cells and may make the patient's body reject them.<sup>21</sup> Increasing number of HLA mismatches has been shown to be associated with poorer graft and patient survival following kidney transplantation.<sup>22</sup> After a kidney transplant, immunosuppressive therapy is used to reduce the risk of rejection of the transplanted kidney (or 'graft') and prolong its survival.<sup>23</sup> Approximately 30% of the patients on transplantation waiting lists currently have evidence of sensitisation in the form of alloantibodies that were generated because of exposure to previous transplants, blood transfusions, pregnancy, or other events.<sup>20</sup>

The presence of a donor-specific positive crossmatch has been considered to be a contraindication to kidney transplantation because of the risk of hyperacute rejection.<sup>10</sup> There are no therapies yet approved for desensitisation, and current protocols often result in incomplete removal of DSA, rebound antibody production, and an increased risk of acute and chronic antibody-mediated rejection, which are the primary causes of early graft loss and return to dialysis, with emotional consequences for the patients and financial consequences for the health care system.<sup>20</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

Moderate to severe CKD affects approximately 5.5% of adults and is more common in older people.<sup>16</sup>

The CKD prevalence model provides estimates of total CKD prevalence for adults aged 16 and over in England. The model was developed using data from the Health Survey for England (HSE) – 2009 and 2010 and the 2011 Census. It is expected that 2.6 million people aged 16 years and older in England have CKD stage 3-5. This is equal to 6.1% of the population of this age group. CKD stage 3-5 prevalence is higher in women than in men, 7.4% versus 4.7%. There is a clear association between increasing age and higher CKD stage 3-5 prevalence; with 1.9% of people aged 64 and under estimated to have CKD stage 3-5, 13.5% of people aged 65-74 and 32.7% of people aged 75 and over.<sup>24</sup>

In 2017-18 there were 36,005 hospital admissions, 52,901 Finished Consultant Episodes, and 19,198 day cases in England for CKD stage 3-5 (ICD 10 Code: N18.5).<sup>25</sup>

Over 3,000 kidney transplants take place every year in the UK. Every day 5 people are added to the transplant list.<sup>26</sup>

For many patients with end-stage renal disease awaiting a kidney transplant, sensitisation to HLA by blood transfusion, pregnancy, or previous transplantation, resulting in circulating antibodies (HLA-antibody or DSA), adversely affects the chances of obtaining a suitable donor organ. In the UK, the level of sensitisation is estimated by the calculated reaction frequency (cRF), which estimates the percentage of deceased donors against whom the recipient has pre-formed anti-HLA antibodies. 26% of patients on the waiting list are highly sensitised, with a cRF of at least 85%; for such patients, transplant waiting time is doubled to a median of 6 years compared with patients with a cRF less than 10%.<sup>27</sup>

In England, the Hospital Episode Statistics in admitted patients records a total of 116 finished consultant episodes (FCEs) and 115 admissions related to pre-transplantation and post-transplantation interventions (OPCS-4 codes M17.2, M17.4, M17.8 and M17.9) and around 3,048 FCEs resulting in 2,747 admissions due to transplantation of kidney (OPCS-4 codes M01). A total of 139 FCEs for excisions of transplanted kidneys amounting to 95 admissions and 1,127 FCE bed days were also recorded for OPCS codes M02.6 and M02.7.<sup>28</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

Kidney transplant is used to treat established kidney failure, which is severe and irreversible impairment of kidney function. Immunosuppressive therapy aims to prevent acute rejection and optimise the function of the transplanted kidney, while minimising the adverse effects of immunosuppression (such as increased risk of infection, cancer, diabetes and cardiovascular disease).<sup>23</sup>

Various attempts that have been designed to improve transplantation rates among highly sensitised patients incorporate the use of desensitisation protocols combining B-lymphocyte-depleting agents (e.g., rituximab and anti-CD20), intravenous immune globulin, and plasmapheresis, combined with better stratification of immunologic risk with the use of sensitive donor-specific HLA-antibody screening and avoidance techniques.<sup>20</sup>

### CURRENT TREATMENT OPTIONS

NICE recommends the following treatment options for prevention of organ transplant rejection:<sup>23</sup>

- Basiliximab, when used as part of an immunosuppressive regimen that includes a calcineurin inhibitor, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant.
- Immediate-release tacrolimus, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant.
- Mycophenolate mofetil, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant.

Currently, there are no approved drugs for desensitisation and the management of donor-specific antibody-induced antibody-mediated rejection.<sup>20</sup>

## PLACE OF TECHNOLOGY

If licensed, imlifidase will offer a treatment for desensitisation of highly sensitised patients undergoing kidney transplantation who have CKD, enabling transplantation in patients with positive crossmatch against an available deceased donor.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	Highdes, <a href="#">NCT02790437</a> , 15-HMedIdeS-06; aged 18 to 70 yrs; imlifidase; phase II
<b>Sponsor</b>	Hansa Biopharma AB
<b>Status</b>	Completed
<b>Source of Information</b>	Trial registry <sup>1</sup>
<b>Location</b>	EU (not incl UK) and USA
<b>Design</b>	Non-randomised, single group assignment, open label
<b>Participants</b>	n=19; aged 18-70 yrs; patients (pts) on the kidney transplant waitlist who have previously undergone desensitisation unsuccessfully or in whom effective desensitisation will be highly unlikely; pts with a live or deceased donor with a positive crossmatch test
<b>Schedule</b>	Pts received one dose of 0.25 mg/kg bodyweight imlifidase on study day 0. If negative crossmatch was not achieved, a second dose could be given within 2 days of the first infusion
<b>Follow-up</b>	180 days
<b>Primary Outcomes</b>	Efficacy [Time frame: Within 24 hours of imlifidase dosing]
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Efficacy on antibodies [Time frame: Within 48 hrs. Time points 2, 6, 24 and 48 hrs after administration of imlifidase]</li> <li>• Efficacy on complement-dependent cytotoxicity (CDC) crossmatch test [Time frame: Within 24 hours]</li> <li>• Efficacy on Flow cytometric crossmatch (FACS) test [Time frame: Within 24 hours]</li> <li>• Safety as assessed by adverse events, clinical laboratory tests, vital signs [Time frame: 180 days]</li> </ul>
<b>Key Results</b>	Not reported
<b>Adverse effects (AEs)</b>	Not reported
<b>Expected reporting date</b>	Previously reported as Dec 2017

<b>Trial</b>	<a href="#">NCT02224820</a> , <a href="#">EudraCT 2013-005417-13</a> , 13-HMedIdeS-02; pts aged 18 yrs and older; imlifidase; phase II
<b>Sponsor</b>	Hansa Biopharma AB
<b>Status</b>	Completed

<b>Source of Information</b>	Trial registry; <sup>4,29</sup> Journal article <sup>20</sup>
<b>Location</b>	EU (not incl UK)
<b>Design</b>	Non-randomised, single group assignment, open label
<b>Participants</b>	N=8; aged 18 yrs and older; pts diagnosed with CKD and in dialysis with identified antibodies against at least two HLA antigens of which at least one is 3000 MFI or more as measured by SAB assay on at least two occasions
<b>Schedule</b>	Pts who underwent transplantation received imlifidase at a dose of 0.24 mg/kg of body weight (USA) or at a dose of 0.25 mg/kg or 0.50 mg/kg
<b>Follow-up</b>	Pts were followed up for 64 days
<b>Primary Outcomes</b>	Efficacy [Time frame: 24 hours]
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Safety [Time frame: 9 weeks]</li> <li>• Pharmacodynamics [Time frame: Up to day 64]</li> <li>• Immunogenicity [Time frame: Up to 64 days]</li> <li>• Pharmacokinetics [Time frame: Up to 21 days]</li> </ul>
<b>Key Results</b>	Outcomes of two independently performed open-label, phase 1–2 trials (conducted in Sweden and the United States) showed that the median calculated panel-reactive antibody level was 96% (range, 82 to 100) in the patients in the U.S. study and 81% (range, 22 to 100) in the patients in the Swedish study. Patients in the U.S. study had a significantly longer cold ischemia time (the time elapsed between procurement of the organ and transplantation), a significantly higher rate of delayed graft function, and a significantly higher mean fluorescence intensity for HLA class I antibodies at the time of transplantation than did those in the Swedish study. A total of 22 of 25 patients had donor-specific antibodies present at the time of transplantation. No patient had detectable HLA antibodies or donor-specific antibodies immediately after transplantation.
<b>Adverse effects (AEs)</b>	In the U.S. cohort, no significant infectious complications were observed. No deaths occurred in this study. A total of 38 serious adverse events were observed in 15 patients; 5 of these events were considered by the investigators as being possibly attributable to imlifidase. There were 13 infectious complications that generally responded to treatment. However, in the Swedish study, 1 patient had prolonged parvovirus B19 viremia and 1 had persistent myalgias after the imlifidase infusion.
<b>Expected reporting date</b>	-

<b>Trial</b>	<a href="#">NCT02475551</a> , 13-HMedIdeS-03; aged 18 yrs and older; imlifidase; phase II
<b>Sponsor</b>	Hansa Biopharma AB
<b>Status</b>	Completed
<b>Source of Information</b>	Trial registry; <sup>30</sup> Journal article <sup>20</sup>
<b>Location</b>	EU (not incl UK)
<b>Design</b>	Non-randomised, single group assignment, open label
<b>Participants</b>	n=10; aged 18 yrs and older; pts diagnosed with CKD and in dialysis with preformed anti-HLA antibodies (non-DSA, DSA or both), negative T-CDC CXM and at least one antibody MFI > 3000

<b>Schedule</b>	The starting dose will be 0.25 mg/kg, given as a single IV infusion prior to surgery with the possibility to increase the dose in higher dose groups.
<b>Follow-up</b>	Not reported
<b>Primary Outcomes</b>	Safety [Time frame: 6 months]
<b>Secondary Outcomes</b>	Efficacy (mean fluorescent intensity (MFI) of less than 1100 as measured in a single antigen bead (SAB) assay) [Time frame: 24 hours]
<b>Key Results</b>	The median calculated panel-reactive antibody level was 96% (range, 82 to 100) in the patients in the U.S. study and 81% (range, 22 to 100) in the patients in the Swedish study. Patients in the U.S. study had a significantly longer cold ischemia time (the time elapsed between procurement of the organ and transplantation), a significantly higher rate of delayed graft function, and a significantly higher mean fluorescence intensity for HLA class I antibodies at the time of transplantation than did those in the Swedish study. A total of 22 of 25 patients had donor-specific antibodies present at the time of transplantation. No patient had detectable HLA antibodies or donor-specific antibodies immediately after transplantation.
<b>Adverse effects (AEs)</b>	In the U.S. cohort, no significant infectious complications were observed. No deaths occurred in this study. A total of 38 serious adverse events were observed in 15 patients; 5 of these events were considered by the investigators as being possibly attributable to imlifidase. There were 13 infectious complications that generally responded to treatment. However, in the Swedish study, 1 patient had prolonged parvovirus B19 viremia and 1 had persistent myalgias after the imlifidase infusion.
<b>Expected reporting date</b>	-

<b>Trial</b>	<a href="#">NCT03611621</a> , 17-HMedIdeS-14; aged 18 yrs and older; imlifidase; observational study
<b>Sponsor</b>	Hansa Biopharma AB
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial registry <sup>31</sup>
<b>Location</b>	EU (not incl UK) and USA
<b>Design</b>	Observational, prospective
<b>Participants</b>	n=46 (planned); aged 18 yrs and older; previous dosing with imlifidase followed by kidney transplantation and participation in one of the following clinical studies: 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 or 15-HMedIdeS-06
<b>Schedule</b>	The study will primarily determine the time of graft survival in subjects who have received imlifidase prior to kidney transplantation. Subjects that have participated, or are currently participating, in the imlifidase kidney transplantation studies (called feeder studies) 13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06 will be included. The subjects will attend 4 follow up visits, 1, 2, 3 and 5 years after imlifidase administration.
<b>Follow-up</b>	5 years
<b>Primary Outcomes</b>	Evaluation of graft survival in subjects who have undergone kidney transplantation after imlifidase administration. [Time frame: 5 years after first dose of imlifidase]

<b>Secondary Outcomes</b>	<p>Time frame: 5 years after first dose of imlifidase</p> <ul style="list-style-type: none"> <li>• Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of patient survival</li> <li>• Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of kidney function (eGFR)</li> <li>• Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of kidney function (P-creatinine)</li> <li>• Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of kidney function (proteinuria)</li> <li>• Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of comorbidities and treatments</li> <li>• Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of quality of life: Health related quality of life (HR-QoL) as evaluated by patient questionnaires EQ-5D-5L</li> <li>• Evaluation of long-term clinical outcomes of transplanted subjects treated with imlifidase in terms of quality of life: HR-QoL as evaluated by patient questionnaires KDQOL-SF</li> </ul>
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Primary completion date reported as Dec 2022

## ESTIMATED COST

The cost of imlifidase is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal guidance. Immunosuppressive therapy for kidney transplant in adults (TA481). October 2017.
- NICE guideline in development. Chronic kidney disease: assessment and management (update). Expected date of publication: July 2020.
- NICE guideline. Renal replacement therapy and conservative management (NG107). October 2018.
- NICE guideline. Chronic kidney disease in adults: assessment and management (CG182). July 2014. Updated: January 2015.
- NICE quality standard. Renal replacement therapy services for adults (QS72). October 2018.
- NICE interventional procedure guidance. Robot-assisted kidney transplant (IPG609). April 2018.
- NICE diagnostic guidance. Multiple frequency bioimpedance devices to guide fluid management in people with chronic kidney disease having dialysis (DG29). June 2017.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013 NHS Standard Contract for adult kidney transplant service. A07/S/a.



- NHS England. Clinical Commissioning Policy: Eculizumab in the treatment of recurrence of C3 glomerulopathy postkidney transplant (all ages). 16054/P. February 2017.

## OTHER GUIDANCE

- British Transplantation Society. Guidelines for Living Donor Kidney Transplantation. March 2018.<sup>32</sup>
- European Association of Urology. European Association of Urology Guidelines on Renal Transplantation: Update 2018.<sup>33</sup>
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of chronic kidney disease: A national clinical guideline (SIGN 103). June 2008.<sup>34</sup>

## ADDITIONAL INFORMATION

Hansa Biopharma AB did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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