William Blair

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Initiation Report

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Hansa Biopharma AB

Turning the TIdeS: Imlifidase Provides a Novel Solution to Widen Transplant Access and Treat Antibody-Driven Acute Diseases

We are initiating coverage of Hansa Biopharma with an Outperform rating, based on the clinical and commercial potential of imlifidase in multiple indications where acute immunoglobin G (IgG) reduction can provide meaningful clinical benefit. The company is currently marketing imlifidase under conditional approval in Europe, sold as Idefirix, and conducting the Phase III ConfIdeS trial to support approval in the United States for the desensitization of highly sensitized patients prior to kidney transplant, with results in 2024. We believe positive ConfIdeS trial results and commercialization in the United States will accelerate the revenue trajectory of Idefirix, where roughly 3,000 patients currently on the kidney transplant waiting list could potentially benefit from Idefirix. We estimate peak sales of SEK 4.7 billion in kidney transplant desensitization alone in 2035.

Imlifidase is differentiated from many other autoimmune drugs targeting pathogenic antibodies by the rapid onset of action, eliminating potentially harmful antibodies within hours of administration. This profile is well-suited for diseases driven by acute autoantibody- or alloantibody-mediated inflammation, and the broad potential was recently highlighted by positive clinical data from Phase II trials with imlifidase in anti-glomerular basement membrane (GBM) disease and antibody-mediated rejection (AMR). Clinical success in anti-GBM and AMR offer near-term expansion opportunities through formal label expansion or compendia listing and off-label usage. We believe the profile of imlifidase will continue to translate into clinical benefit for patients in additional indications, including GBS and removing neutralizing antibodies in patients prior to gene therapy, where proof-of-concept results in the next 12 to 18 months will lead to advancement to pivotal trials. Overall, the combination of these indications gives imlifidase blockbuster potential, and we currently derive a fair value for shares of SEK 160. Hansa recently disclosed plans to initiate the first clinical trial with the company's next-generation therapy, HNSA-5487, which has the potential to be re-dosed, thereby supporting utilization in an even broader set of diseases driven by IgG antibodies. While we do not include this program in our estimates given the stage of development, positive proof-of-concept results in initial clinical studies would be a significant value driver.

Key risks for Hansa include clinical and regulatory risk, with heavy reliance on a single product for success. The company is also subject to commercial risk and the need for imlifidase to be incorporated into treatment guidelines and organ allocation systems.

Hansa Biopharma is focused on the development of the IgG-cleaving enzyme imlifidase for serious diseases driven by IgG antibodies. Marketed as Idefirix in Europe, the therapy has received conditional approval for desensitization of patients prior to kidney transplantation, with ongoing trials in kidney transplant and other indications.

Stock Rating:	**Outperform**
Symbol:	HNSA (STO)
Price: SEK 47.06 (52-Wk.: SEK 45– SEK 106)	
Market Value (mil.):	SEK 2,470
Dividend/Yield:	None
Fiscal Year End:	December

Estimates	**2022A**	**2023E**	**2024E**
EPS FY (SEK)	13.57	14.36	11.80
Sales (SEK, mil.)	154.5	171.7	341.9

Valuation			
P/E	NA	NA	NA

Trading Data	
Shares Outstanding (mil.)	52.4
Average Daily Volume	212,107

Financial Data	
Total Debt (SEK, mil.)	798
Total Cash (SEK, mil.)	1,286
Enterprise Value (SEK, mil.)	1,981

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Valuation and Investment Summary

We are initiating coverage of Hansa Biopharma with an Outperform rating based on the potential of the company's lead program, imlifidase (marketed as Idefirix in Europe), across a number of indications that can benefit from rapid reduction in the presence of aberrant immunoglobulin G (IgG). While the most near-term inflection point is the pivotal results from the Phase III trial of imlifidase in patients who are highly sensitized prior to kidney transplant, which should support regulatory approval in the United States, we see indication expansion over the next 12 to 24 months as driving additional upside from the commercial opportunity across indications.

Imlifidase has demonstrated the ability to rapidly and completely eliminate IgG antibodies in humans, across healthy volunteers, patients who are highly sensitized to potential donor tissue, patients with anti-GBM antibodies, and patients experiencing AMR. We believe this mechanism of action will continue to translate across indications, such as for removal of antibodies that could potentially neutralize gene therapies, and believe it is just matter of finding the indications where a one-time removal of IgGs can drive clinical benefit. While not part of our current investment thesis, the ability to repeatedly remove IgGs through repeat dosing without development of antidrug antibodies (ADAs) to the enzyme itself, which is the goal of the company's NiceR program and lead candidate HNSA-5487, has the ability to significantly expand the number of indications that Hansa can explore with this platform technology.

Multiple Phase II Studies With Imlifidase in Highly Sensitized Patients Prior to Kidney Transplantation Have De-risked the Phase III ConfIdeS Trial

Significant research and resources have been utilized in improving the outcomes of patients with end-stage renal disease (ESRD), with numerous studies demonstrating the benefits on quality of life and survival in patients able to receive a kidney transplant versus remaining on dialysis.

Despite the overwhelming benefit of transplantation, up to one-third of patients in developed nations remain on the waitlist for many years and often become ineligible for a donation prior to receiving a compatible donor match; this is due to the existence of donor-specific antibodies (DSAs) that would cross-react with the donor kidney, resulting in hyperacute rejection and graft failure. While changes in kidney allocation systems, particularly in the United States, have prioritized finding compatible donors for these patients, the percentage of highly sensitized patients on the waitlist remains significant. In addition, as more kidney transplants are performed every year across age groups, we believe more patients are likely to eventually need a second kidney transplant, at which point the patient will be more sensitized to donor tissue than previously, potentially expanding the market opportunity longer term.

The use of imlifidase to remove DSAs in a patient prior to organ transplantation has been evaluated in multiple clinical studies. Summarized in detail in this report, these studies have overwhelmingly shown the ability of imlifidase to rapidly remove IgG DSAs, resulting in crossmatch negative status within hours of imlifidase treatment. While the numerous complications of organ transplantation mean not 100% of patients in the trials have been successfully transplanted, the 98% success rate to date across three studies is highly encouraging versus what has been achieved with other desensitization protocols. In particular with deceased-donor transplantations, which must be completed within hours of organ procurement, the rapid effect of imlifidase treatment is the optimal preconditioning for these patients, combined with other standard-of-care regimens to reduce DSA rebound and cellular immunity.

Imlifidase received conditional approval from the EMA in 2021, under the brand name Idefirix, and is currently in a Phase III study in the United States (ConfIdeS) and a confirmatory trial in Europe. Based on the available data to date from Phase II trials and the design of the Phase III ConfIdeS

trial, we expect positive results from the study in 2024 to show statistically significant benefit in renal function at one year after imlifidase treatment and deceased-donor kidney transplantation, compared to patients treated with available standard of care. We estimate 95% of patients will be successfully transplanted in the imlifidase arm, with 90% of those transplanted having a surviving graft by one year of follow-up. We expect minimal patients in the control arm to be able to successfully receive a transplant based on the enrollment criteria in the trial, but for this analysis we assume roughly 10% may successfully receive a transplant. Patients not receiving transplant will be assumed to maintain dialysis, and therefore would be considered as having an estimated glomerular filtration rate (eGFR) of zero at one year (per the analysis plan of the trial). We assume patients with no delayed graft function will have an eGFR of 60 at one year, those with delayed graft function will have an eGFR of 40 to 50, and those with graft failure will be on dialysis with an eGFR of zero. Therefore, we estimate an eGFR across all patients in the ConfIdeS trial of 48 mL/min/1.73 m^2 versus 3 mL/min/1.73 m^2 in the control arm. While this analysis involves a lot of assumptions based on Phase II trials, we believe it demonstrates the benefit of successfully getting patients to transplant and the large margin in eGFR at 12 months between the two treatment arms.

Although the commercial ramp-up in Europe has been gated by government reimbursement timelines and the need to educate physicians and treatment centers, we believe the launch of imlifidase will accelerate in 2025 and beyond following approval in the United States and continued momentum from positive physician experience and data generated from the ConfIdeS trial.

We assume that patients with a calculated panel reactive antibody (cPRA) of 98% or greater will be the ideal patient population for imlifidase, with other factors such as time on waitlist and patient comorbidities determining the patients best suited for the desensitization therapy. Given the enrollment criteria of the ConfIdeS trial, it is unclear if a potential labeled indication for imlifidase from the FDA would specify cPRA levels of 99.9% or greater (the cut-off for enrollment in ConfIdeS) or would be more ambiguous by stating highly sensitized patients. At this time, our estimates are based on penetration into patients with a cPRA of 99.9% or above, or roughly 3% to 5% of patients on the waiting list in the United States. We also assume imlifidase in the United States will be priced at a premium to Idefirix in the European Union, at roughly $425,000 per patient. With a peak penetration of 20% of kidney transplants annually, we estimate peak sales in the United States of $324 million (SEK 3.376 million; 10.40 SEK to USD exchange ratio used through this report) by 2035.

Phase II Results Anti-GBM Provide Next Expansion Opportunity for Imlifidase

Anti-GBM disorder is a rare kidney disease, where antibodies directed against an antigen on the noncollagenous domain of type IV collagen protein present on the GBM leads to acute kidney injury, potentially leading to dialysis and requirement for kidney transplant.

Anti-GBM has had little by way of clinical development over the last 40 years. The current standard of care involves the use of high-dose steroids and cyclophosphamide to prevent continued autoantibody production, followed by numerous cycles of plasma exchange (PLEX) to remove autoantibodies from the circulation. The use of PLEX has decreased mortality and improved renal survival in the disease, but its onset of action is relatively slow and the key to preventing renal damage involves rapidly reducing circulating autoantibodies. The mechanism of action of imlifidase with its rapid ability to clear these autoantibodies therefore makes sense in the setting.

Data from an investigator-led study of imlifidase in anti-GBM showed that 10 patients (67%) were dialysis independent at 6 months, with a further patient becoming dialysis independent at 8 months following treatment with imlifidase—taking the one-year renal survival rate to 73%. Acknowledging the caveats of cross-trial comparisons, these initial data look favorable compared to matched historical controls (see exhibit 25).

Hansa initiated the Phase III GOOD-IDES-02 study for imlifidase in the fourth quarter of 2022, with the first patient expected to be dosed in the first half of 2023. The open-label study aims to recruit 50 patients with anti-GBM from 30 to 40 clinics worldwide, who will be randomized 1:1 to either imlifidase plus SoC of PLEX, cyclophosphamide and steroids, or SoC alone.

Anti-GBM is rare, occurring in about 500 patients per year in the United States, but there is little competition in terms of additional clinical development. We believe that approval in 2026 could lead to peak sales in the United States of $72 million (SEK 749 million) in 2035.

AMR Phase II Study Met Its Primary Endpoint With Clarity on Further Development Expected This Year

AMR refers generally to the acute rejection of the donor organ, such as a kidney, resulting from a host humoral immune response, often resulting in the destruction of the graft. AMR has been cited as the most common cause of immune-mediated allograft loss, and acute AMR has been shown to occur in 5% to 7% of kidney transplants annually, with higher rates in those with pre-existing DSAs. Some estimates of AMR implication in graft loss are as high as 57% to 63%, meaning AMR represents a significant challenge for the transplant field.

There are currently no approved therapies for AMR, and KDIGO guidelines note that the optimal treatment approach for acute humoral rejection is yet to be fully determined. Indeed, there have been no large, randomized, controlled trials comparing the safety and efficacy of different therapeutic strategies for AMR. Combination strategies are most often employed to inhibit B-cell maturation and activity, though there is no real consensus on the best means of treating AMR. Patients are most commonly treated with intravenous immunoglobulins (IVIg) or plasmapheresis, with other options such and rituximab and anti-T-cell antibodies also being employed.

Like anti-GBM, the main goal of treatment is the rapid removal of donor-specific antibodies (followed by suppression production and activation of the immune cells responsible), making treatment with imlifidase a rational component of the therapeutic approach. Hansa announced in November 2022 that a Phase II study of imlifidase in AMR met its primary endpoint of superior reduction in DSAs versus plasmapheresis, with full results from the study expected in the second half of 2023. Following the Phase II results, management plans to disclose next steps for the AMR program, but given that many regulatory bodies have historically relied on hard renal outcomes in this setting, a meaningful investment may be required for a Phase III study. If earlier timepoints are not a possibility near term, we believe Hansa may hold off on an official Phase III study, in which case utilization in AMR would likely still occur through off-label utilization following physician comfort gained in the transplant setting. CSL Behring's Phase III study for IL-6 antibody clazakizumab could provide some context for a design, with the company hoping to support an accelerated approval with 52-week eGFR data ahead of a confirmatory endpoint of allograft loss.

Over the life of a kidney transplant, an estimated 5% to 7% of patients will experience AMR. This includes both acute AMR and chronic AMR, and patients who are sensitized at the time of transplant have a much higher risk of an AMR episode (over 20%). We assume roughly 1,500 patients per year will require treatment for AMR, and roughly a quarter of these episodes will be severe acute reactions, which are the ideal patient for imlifidase treatment given the rapid onset of action and cost of the therapy. Assuming half of these patients are treated with imlifidase, we estimate a peak sales opportunity of $89 million (SEK 929 million) in the United States.

Additional Indications in GBS and Gene Therapy

Although we base the majority of our investment thesis on the use of imlifidase in desensitization prior to kidney transplant, treatment of AMR (particularly acute AMR), and anti-GBM disease, we believe clinical results in Guillain-Barré syndrome (GBS) and gene therapy preconditioning have the potential to quickly increase the total market opportunity for imlifidase.

A Phase II trial in GBS is currently ongoing, and although the COVID-19 pandemic disrupted the pace of clinical trial enrollment, Hansa announced on March 31 that the trial had completed enrollment, confirming timelines for initial top-line data in the second half of 2023. While we do believe imlifidase will again result in rapid clearance of pathogenic IgG antibodies from circulation, it is difficult to make assumptions on what a Phase III program in GBS would entail given the lack of regulatory precedence. We base our current assumptions on the Phase III trial of ANX005, an antibody targeting C1q of the complement system, which is currently in a Phase III trial in GBS patients. The trial is enrolling over 200 patients across three arms, two doses of ANX005 and placebo, with a primary endpoint of GBS disability score at week 8. We discuss this trial in greater detail in this report.

Given we assume around 3,300 patients in the U.S. each year will experience GBS, the opportunity in the setting is one of the larger ones for imlifidase. With that said, we do think the study is higher risk, and therefore model a lower probability of success in the setting at this time. We model approval in 2028 and peak sales of $473 million (SEK 4,919 million) in 2035 in the United States.

For the use of imlifidase as a preconditioning to gene therapy, Hansa has two collaborations ongoing, with Sarepta and AskBio, with the first clinical study evaluating imlifidase with SRP-9001 in Duchenne muscular dystrophy (DMD) patients on track to begin clinical trials in 2023. The potential of gene therapy has sparked significant industry interest and clinical development, yet preexisting antibodies to viral capsid proteins may preclude up to 50% of patients from potentially receiving these life-altering therapies. Preclinical work from third parties has provided initial proof-of-concept data, and Hansa has disclosed supportive preclinical data with SRP-9001 will be presented at an upcoming medical conference. In regard to the Sarepta collaboration, successful clinical data would be highly lucrative for Hansa in the form of $397.5 million in potential development, sales, and regulatory milestones, royalties on sales in patients requiring imlifidase pretreatment, and booking sales from imlifidase utilization. Although only 14% of DMD patients are expected to have preexisting antibodies to the SRP-9001 viral vector, we believe the opportunity will expand over time with additional development programs, such as Sarepta's program in limb-girdle muscular dystrophy, and imlifidase may ultimately allow the retreatment of patients with a second gene therapy longer term.

Sarepta's SRP-9001 is currently under regulatory review with a PDUFA date of May 29, 2023. FDA accelerated approval of SRP-9001 would likely accelerate the development of imlifidase plus SRP-9001 in patients with preexisting neutralizing antibodies, and therefore would be a positive for Hansa.

NiceR Program Entering the Clinics Provides Significant Upside if Proof-of-Concept Data Are Positive

Despite the benefits of imlifidase treatment, the bacterial derived enzyme does elicit a robust humoral immune response in patients, which would likely neutralize subsequent activity upon retreatment or potentially result in anaphylactic reaction. Hansa has been working for nearly a decade on the development of a next-generation version of imlifidase, capable of rapidly removing pathogenic IgG antibodies yet not eliciting a robust immune response, and therefore capable of being administered more than once, providing prolonged or repeated IgG removal.

The removal of immunogenic amino acid sequences is a difficult process, given the difficulty in predicting what sequences may become immunogenic upon amino acid changes and ensuring the enzymatic activity and specificity of the enzyme is maintained. Limited disclosures have been made on this program to date, but management has disclosed lead program HNSA-5487 will begin a healthy volunteer study in 2023, and the profile will determine subsequent clinical development, such as in additional transplant indications (hematopoietic stem cell) or autoimmune diseases.

A summary of our NPV for Hansa Biopharma is shown in exhibit 1.

Exhibit 1
Hansa Biopharma AB
Overview of Valuation Analysis

Program	Indication	U.S. Commercial Launch	Peak penetration (U.S.)[1]	Peak U.S Sales ($, k)	Peak Worldwide Sale (SEK, k)	Probability of Success	NPV (k)	NPV/Share
Idefirix	Kidney Transplant	2025	20%	$324,619	4,650,763 kr	81%	4,981,121 kr	93.57 kr
Idefirix	Anti-GBM	2026	50%	$72,070	1,762,617 kr	68%	630,440 kr	11.84 kr
Idefirix	AMR	2026	50%	$89,342	1,256,816 kr	64%	736,689 kr	13.84 kr
Idefirix	GBS	2028	30%	$472,944	10,107,396 kr	30%	2,155,501 kr	40.49 kr
						Sum	8,503,750.61 kr	159.74 kr

Source: William Blair Equity Research

Company Overview

Background

Hansa Medical Utvecklings AB was founded in 2001 based on the discovery of the IdeS enzyme by Professor Lars Bjorck at Lund University. Following the first preclinical model studies with IdeS and securing patents, Hansa Medical AB was formed and acquired Hansa Medical Utvecklings AB, initially listed on the Nasdaq First North exchange. While other programs at the company also evaluated diagnostics for sepsis and therapeutics for rheumatoid arthritis, those programs were outlicensed and focus was placed on imlifidase development. In 2015, the company's shares were listed on the Nasdaq Stockholm exchange under the ticker HNSA.

The specificity and rapid effect of imlifidase on IgG antibodies created an opportunity to utilize the enzyme as a therapeutic intervention, with preclinical success across multiple disease models. The clinical development plans focused on desensitizing human leukocyte antigen (HLA)-immunized patients prior to kidney transplant and treatment of antibody-mediated organ rejection, although additional preclinical work and investigator-sponsored studies have expanded the potential indications, as summarized in this report.

Pipeline

Hansa's pipeline currently focuses on the numerous opportunities for imlifidase across multiple autoantibody-driven diseases. The company is pursuing next-generation versions of imlifidase in the NiceR program with the aim of facilitating retreatment, with plans to pursue development in autoimmune disease, transplant, and potentially oncology. The company is also developing the EnzE program, aimed at improving outcomes with cancer immunotherapy. A summary of ongoing programs is shown in exhibit 2 on the following page.

Management

We outline key members of the Hansa Biopharma management team in exhibit 3 on page 10. The most important recent management hire was Matthew Shaulis as chief commercial officer. Idefirix has had a relatively steady start to commercialization in Europe as the company works through reimbursement on a country-by-country basis, but Shaulis brings 20 years of U.S. biotech and pharma marketing experience to Hansa, including eight years at Pfizer as president of Pfizer Oncology North America and president of international developed market for the inflammation and immunology franchises, which Hansa hopes to leverage as it moves toward a U.S. launch for imlifidase. The company also recently announced plans for Chief Scientific Officer Christian Kjellman to leave the company in 2024. Given the advancement of the company to focus on clinical and commercial execution and with a lead candidate from the NiceR program selected, Dr. Kjellman's departure makes sense from a timing perspective, and his staying with the company into 2024 should provide for the transfer of technical expertise in a timely manner.

Exhibit 2
Hansa Biopharma AB
Pipeline

Candidate	Preclinical	Phase I	Phase II	Phase III	Marketing authorization	Marketed	Status	Anticipated Milestones/Catalysts
Imlifidase								
EU: Kidney transplantation in highly sensitized patients							-Commercialization ongoing	-Post approval study to be completed by 2025
U.S.: Kidney transplantation in highly sensitized patients							-Clinical Phase III ongoing	-Completion of enrollment (64 patients) first half 2023
Anti-GBM disease							-Clinical Phase III ongoing	-First patient enrolled (50 patients)
Antibody mediated kidney transplant rejection (AMR)							-Clinical Phase II ongoing	-Full data read-out H2 2023
Guillain-Barre syndrome (GBS)							-Clinical Phase II ongoing	-First clinical readout in second half 2023
Pretreatment ahead of gene therapy in Duchenne muscular dystrophy (partnered with Sarepta)							-Preclinical research ongoing	-Initiate clinical study of imlifidase as pretreatment in DMD 2023
Pretreatment ahead of gene therapy in limb-girdle muscular dystrophy (partnered with Sarepta)							-Preclinical research ongoing	
Pretreatment ahead of gene therapy in Pompe disease (partnered with AskBio)							-Preclinical research ongoing	
NiceR								
Recurring treatment in autoimmune disease, transplantation and oncology							-Preclinical research ongoing	-Initiated Phase I study of HNSA-5487 (Lead NiceR candidate)
EnzE								
Cancer immunotherapy							-Research phase	

Key: **Ongoing** **Completed** **Planned**

Source: Hansa Biopharma company reports

Exhibit 3
Hansa Biopharma AB
Core Management Team

	Role	Started Role	Prior Experience	
Soren Tulstrup	President and CEO	2018	**Senior Advisor to the Chairmanship of FTSE 250 Pharma Company & Private Equity Firms**, 2016-2018 **Senior Vice President, Global Franchise Head (Rare Diseases)** 2012 - 2014 **Multiple incl. Vice President, Global Human Health (Diabetes & Obesity Franchise)** 1996 - 2008	**Chief Executive Officer** 2014 - 2016 **Chief Executive Officer** 2008 - 2012 **Regional Head** 1993 - 1996
Donato Spota, M.B.A.	Senior Vice President, Chief Financial Officer	2019	**Multiple incl. CFO** 2002 - 2019	
Matthew Shaulis, M.B.A.	Chief Commercial Officer and President of the U.S. affiliate	2023	**President, International Developed Markets, Inflammation & Immunology** 2018 - 2023 Multiple incl.Head of Oncology Sales & Strategic Customer Group, 2010-2015	**Multiple incl. President, North America** 2015-2018 Head of Oncology Marketing, 2007-2010
Achim Kaufhold, M.D.	Senior Vice President, Chief Medical Officer, ad interim Chief Scientific Officer	2020	**Chief Medical Officer** 2010 - 2017 **Pharmexa A/S Chief Medical Officer** 2007 - 2008 **Berna Biotech AG (now Johnson & Johnson)** Chief Medical Officer 2001-2005	**Affitech (merged with Pharmexa A/S) CEO** 2008-2009 **Chiron (acquired by Novartis) Chief Medical Officer** 2005 - 2006 **Head of Pediatric Vaccine Development** 1994 - 2001

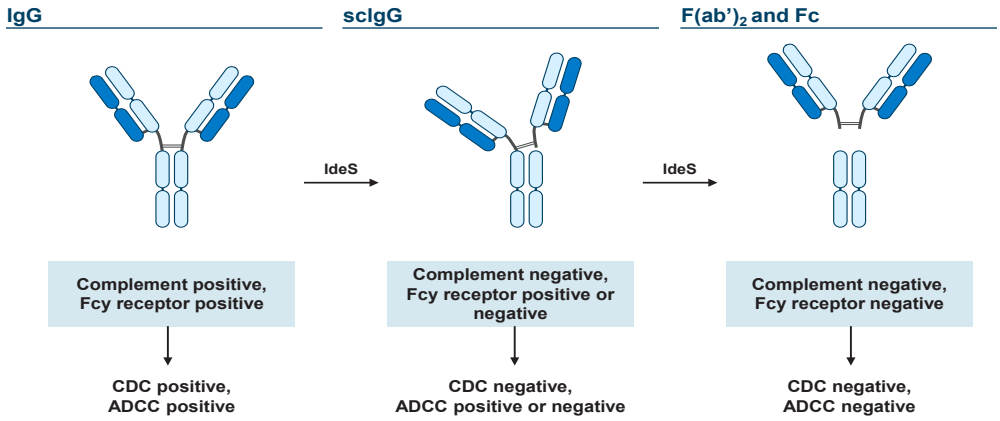
Source: Hansa BioPharma company reports

Imlifidase Background

IdeS (immunoglobulin G-degrading enzyme of *Streptococcus pyogenes*) is a highly specific cysteine protease capable of rapidly cleaving and deactivating human IgG. The 34.9 kDa protease was first described in a 2002 publication (von Pawel-Rammingen U et al., 2002. *EMBO J.*) and determined to be a virulence factor, allowing *S. pyogenes* to counter humoral response by cleaving and deactivating opsonizing IgG antibodies bound to the bacterial surface, preventing antibody mediated phagocytosis. Unlike SpeB, another cysteine proteinase isolated from *S. pyogenes*, IdeS is highly specific for IgG and does not cleave other immunoglobulin subclasses such as IgM, IgA, IgD, or IgE. IdeS does have slightly less activity for the IgG2 subclass of IgG, although given the total reductions of IgG observed in clinics to date, this appears to be inconsequential.

IdeS initially binds to the Fc portion of IgG, then the first reaction is a very rapid and efficient cleavage of one of the two heavy chains at the hinge region at glycine residue 237. The resulting single cleaved IgG molecule still has one heavy chain intact, and cleavage of the second heavy chain is less rapid and less efficient. However, complement C1q binding is largely inhibited after the initial cleavage, resulting in rapid reduction in the effector function of IgG antibodies. Cleavage of the second heavy chain hinge region results in 1 F(ab')2 and 1 homodimeric Fc fragment, as shown in exhibit 4. The initial binding to the Fc portion of IgG as a requirement for cleavage increases substrate specificity over other Ig subtypes.

Exhibit 4
Hansa Biopharma AB
Proteolytic Cleavage



Source: Lena Winstedt et al., 2015. *PLoS One*

Mechanism of Action of Autoantibodies

To understand the potential of IdeS to treat autoimmune disorders, it is essential to understand the process of antibody-driven autoimmune diseases. While this will not be a comprehensive overview of the process, particularly the wide range of triggers for autoantibody production, we briefly summarize antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Both ADCC and CDC are mediated through the Fc domain of immunoglobulins, with different Ig classes and subtypes having different affinities for ADCC and CDC activity.

ADCC is the process of immune cell recognition of antibodies bound to a target antigen through Fc receptors (FcRs) on the surface of the immune cell, typically resulting in activation of the immune cell and cell-mediated destruction of the target cell. IgG is often considered the main Ig subclass involved in ADCC, but IgA and IgE can also elicit ADCC activity. The process is primarily a key part

of the humoral immune response, designed to limit and contain infections, but can result in autoimmunity when the target antigen is expressed on healthy tissues. There are several classes of FcRs in both humans and mice, which are distinguished in their antibody affinity, cellular expression pattern, and downstream signaling effects. In humans, there are five activating FcRs: the high-affinity FcγRI (CD64), and lower-affinity molecules FcγRIIA and FCγRIIC (CD32), and FcγRIIIA and FcγRIIIB (CD16). Activating receptor signaling through the phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) leads to downstream effector functions such as ADCC and antibody-dependent cellular phagocytosis (ADCP).

CDC is the process by which antibodies bound to a surface antigen on a target cell recruit proteins from the classical complement pathway to drive target cell lysis. The first step in this process is the binding of the protein C1q to the Fc domain of the antibody, with IgG1, IgG3, and IgM antibodies eliciting the strongest CDC activity. The binding of C1q triggers a cascade of additional complement protein binding, resulting in C3b deposition on the target cell and the formation of the membrane attack complex (MAC), which opens pores in the membrane of the target cell for lysis.

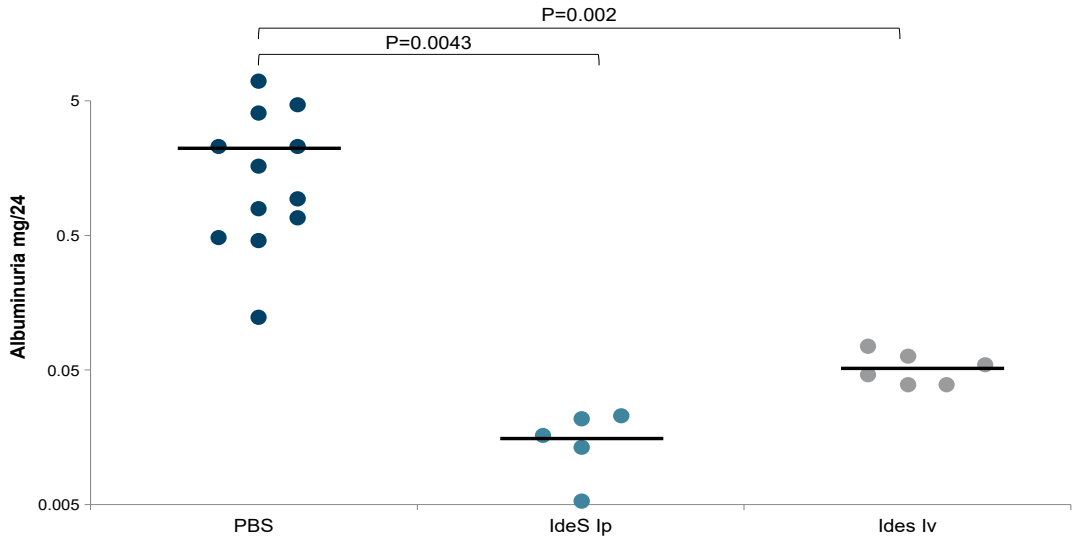
The removal of autoantibodies has therefore been explored as a mechanism to stop or slow the progression of numerous autoimmune diseases. Numerous mechanisms including B-cell depletion, plasmapheresis, immunoadsorption, and increased antibody degradation (FcRn inhibition) are currently utilized across diseases, although a key limitation is that often the rate of antibody removal and level of reduction may not be sufficient for many autoimmune diseases.

Preclinical Data

Various preclinical models demonstrated the ability of IdeS to rapidly remove tissue targeting antibodies capable of driving autoimmune diseases. As an example, Nandakumar et al. published the results of an IdeS treatment in a collagen antibody-induced arthritis mouse model (*Arthritis Rheum*, 2007). In the experiment, IdeS was given three hours prior to the injection of the collagen II–specific antibody cocktail. Mice receiving IdeS were completely protected from clinical or histologic evidence of arthritis, versus 83% of mice developing arthritis in the control group not treated with IdeS. However, in a collagen-induced arthritis model, where Collagen type II is injected into the mice, IdeS treatment on days 22, 26, and 30 post–Collagen type II injection was able to delay, but not prevent, the onset of arthritis. This is not surprising given IdeS is capable of cleaving antibodies in circulation or bound to tissue, but not prevent production of additional autoimmune-inducing antibodies.

In a model of anti-GBM published by Yang et al. in 2010 (*Nephrol. Dial. Transplant*), rabbit anti-GBM antibodies were injected into mice, followed by a mouse antibody against rabbit IgG, and then treatment with placebo, IdeS, or EndoS, a separate *S. pyogenes* enzyme capable of hydrolyzing asparagine-linked glycans on the heavy chain of IgG, thereby reducing C1q and FcγR binding. This model was specifically designed to investigate the ability of IdeS to cleave anti-GBM antibodies already bound to the glomerular basement membrane, since the anti-rabbit IgG is injected seven days after the administration of rabbit anti-GBM antibodies, at which point there are no detectable rabbit IgGs in circulation. Mice in the IdeS treatment group were administered the enzyme at day 6, one day before anti-rabbit antibodies, whereas mice receiving EndoS were given it on day 7, immediately preceding anti-rabbit antibody injection. IdeS treatment completely prevented albuminuria in mice, compared to profound albuminuria in control mice (see exhibit 5). Immunohistochemistry of the kidneys after treatment showed IdeS-treated mice had only trace amounts of intact anti-GBM antibodies bound to the surface, compared to significant antibody presence in control mice. In comparison, EndoS-treated animals did have a significant reduction in albuminuria versus control, but still had elevated albuminuria over baseline. There was also no significant difference in deposition of mouse IgG or complement factors between EndoS- and placebo-treated mice. Importantly, this experiment clearly demonstrates the ability of IdeS to cleave auto-antibodies even when the variable domain is bound to the target antigen on tissues.

Exhibit 5
Hansa Biopharma AB
Albuminuria in Mouse Anti-GBM Model following IdeS Treatment



Source: Yang et al., 2010. *Nephrol. Dial. Transplant*

Last, we highlight a publication by Tradtrantip et al. (*Molecular Pharmacology*, 2013) evaluating IdeS in a model of neuromyelitis optica (NMO) driven by anti-aquaporin 4 (AQP4) autoantibodies. In the in vivo model, IgG antibodies targeting AQP4 were injected intracerebrally into mice in combination with human complement, resulting in marked loss of AQP4, GFAP, and myelin around the injection site by three days. When IdeS was administered in conjunction with the injections, either at the same time as antibody injection or three days later in conjunction with complement injection, lesion size was greatly reduced. In addition, it was found that AQP4 antibody fragments after cleavage by IdeS can compete with pathogenic antibodies and also result in reduced lesion size.

Healthy Volunteer Study

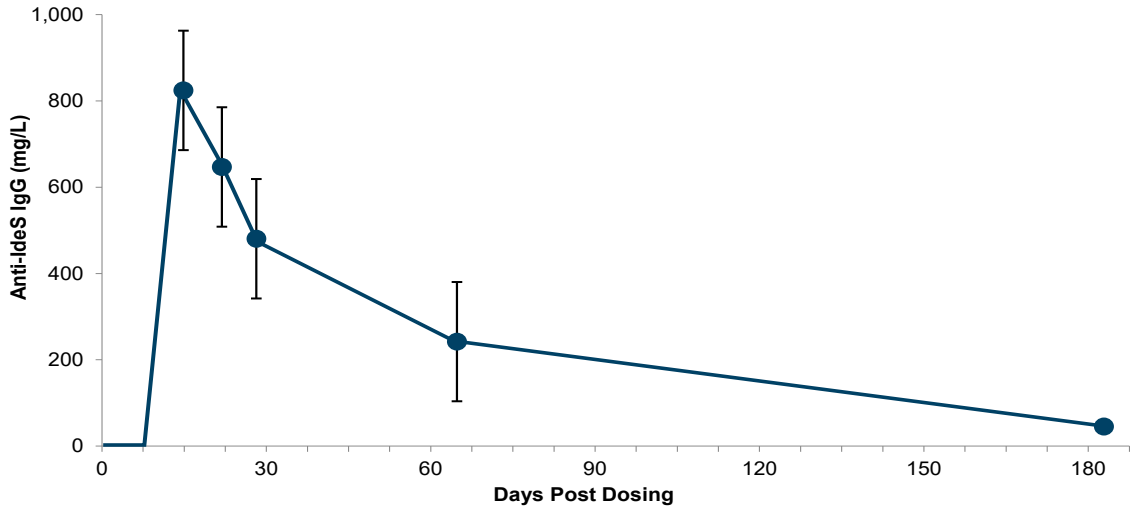
Pharmacokinetics (PK) and pharmacodynamics (PD). In a Phase I trial of intravenous imlifidase in healthy volunteers, patients were randomized to single ascending doses of imlifidase or placebo (Winsedt et al., 2015. *PLOS One*). The selected starting dose was 10 times below the preclinically determined, minimally anticipated biological effect level (MABEL) at 0.01 mg/kg. The trial utilized gradual dose escalation following evaluation of each dose level by a data monitoring committee, increasing to 0.04 mg/kg, 0.12 mg/kg, and 0.24 mg/kg. All healthy volunteers were treated prophylactically with antibiotics until plasma IgG levels returned to greater than 4.5 g/L. Imlifidase has a half-life of 4.9 hours at 0.24 mg/kg, with the majority of the drug eliminated by 24 hours. Imlifidase resulted in full effect within roughly six hours of administration at doses of 0.12 mg/kg to 0.24 mg/kg, rapidly reducing serum IgG levels by 95% from baseline. The generation of new IgG molecules is evident within one week of treatment, returning to baseline levels within three weeks.

Safety profile. The side effect profile of imlifidase was largely benign, with only one patient experiencing grade 2 adverse events consistent with infusion-related reactions. The patient's symptoms resolved within 15 minutes of antihistamine and corticosteroid administration, and the imlifidase infusion was not interrupted. The most common side effect was nasopharyngitis, which occurred in 10 of 20 imlifidase-treated subjects and 6 of 9 patients on placebo. However, dose-dependent,

transient proteinuria was observed after 24-48 hours in subjects who were administered imlifidase, likely a result of clearance of the IgG cleavage products from circulation. There was no difference in proteinuria between imlifidase and placebo patients by day 7.

Immunogenicity. Healthy volunteers were screened for IdeS antibodies (from prior *S. pyogenes* infection), with elevated IgG antibody titers of 15 mg/L being an exclusion criterion. Separate from the individuals screened for this study, a reference group of 130 people were screened for anti-IdeS levels, with 10 out of 130 having levels below 2.0 mg/L, and the median was 6.1 mg/L. In the healthy volunteer study, 78 subjects were screened and all had detectable IgG against IdeS. The median level was 10.6 mg/L, and 28% had anti-IdeS antibodies over 15 mg/L. After imlifidase administration, anti-IdeS IgG levels dramatically increased by day 14, reaching a median of 104 mg/L (range 23.1 mg/L to 1,744.0 mg/L). As shown in exhibit 6, the mean level of anti-IdeS IgG antibodies returned to the normal baseline range by day 182.

Exhibit 6
Hansa Biopharma AB
Kinetics of Anti-IdeS Antibodies in Serum



Source: Winsedt et al., 2015. *PLoS One*

Kidney Transplant Background

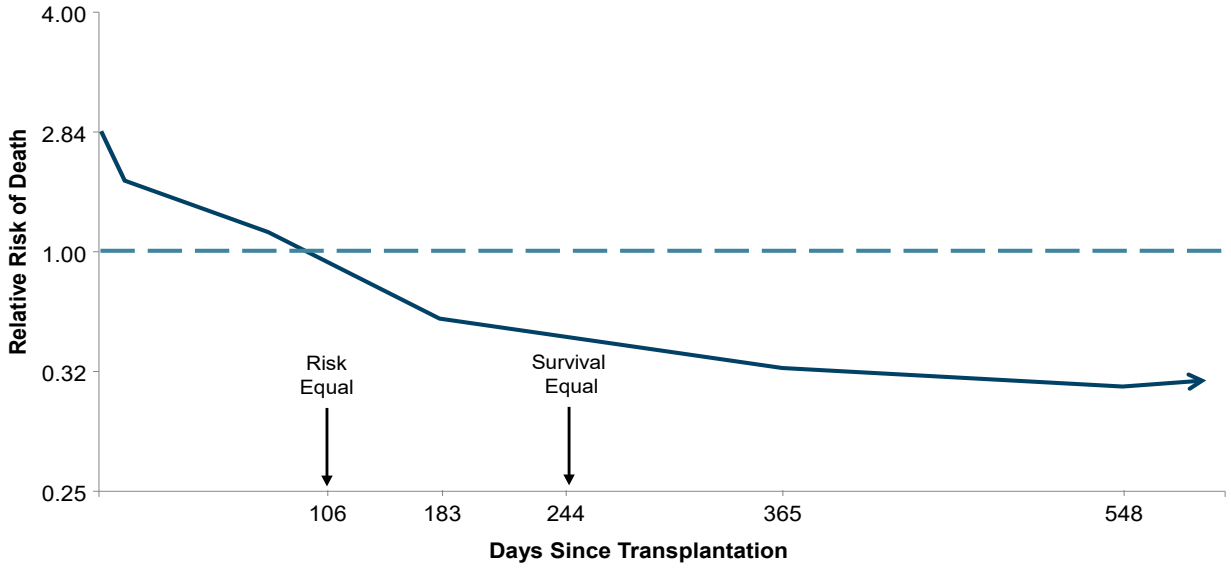
There are numerous causes of ESRD, which is a term used to essentially describe the inability of a patient's kidneys to filter wastes and excess fluids from the blood. This results in dangerous levels of fluid retention, electrolytes, and other waste products accumulating in the body, which can be life threatening if not treated. ESRD can be caused by numerous diseases and conditions, including diabetes, high blood pressure, nephritis (either glomerular or interstitial), or an inherited kidney disease. Patients with ESRD have limited options; either maintenance dialysis, which is associated with co-morbidities and increased mortality, or receiving a kidney transplant. Successful kidney transplantation significantly improves patient quality of life and reduces the risk of mortality, but also creates significant challenges with finding a potential donor kidney and post-transplant monitoring while on immunosuppressive regimens.

A seminal study published in the *New England Journal of Medicine* in 1999 compared the outcomes of patients on dialysis awaiting transplantation versus those who received a deceased-donor transplant utilizing data from the U.S. Renal Data System (Wolfe et al., 1999. *New Engl. J. Med.*). Given patients had historically only been referred to transplant if they were younger, healthier, and of higher socioeconomic status, there was a bias in previous studies comparing patients who were transplanted to those who stayed on dialysis and never were considered for transplant. The study from Wolfe et al. utilized the U.S. Renal Data System, wherein over 228,000 patients under the age of 70 with ESRD were followed from 1991 to 1996. Of these patients, 46,000 were placed on the transplant waiting list, and 23,275 received a first deceased-donor transplant by December 31, 1997.

As shown in exhibit 7, the study found that mortality in the patients who received a transplant was meaningfully higher for the first 106 days following transplant, but then dropped below patients who remained on the waitlist thereafter. The initial increase is due to complications with the transplantation surgery, but by day 244 the overall risk of death had returned to neutral among the groups, with the transplantation group being favored long term. The long-term mortality risk for transplant recipients was estimated to be 68% lower than patients remaining on the waiting list. For patients on dialysis that were not added to the transplant waitlist, the unadjusted annual death rate was 16.1, significantly higher than those on dialysis but added to the waitlist (6.3), a sign of the eligibility requirements for healthier patients to be placed on the waitlist. Those that were added to the waitlist and received a transplant had an annual death rate of 3.8.

The publication by Wolfe et al. resulted in growth of the transplant waitlist, particularly in patients in the older age groups (over 50), which resulted in the need for a greater number of donor kidneys and a better allocation system to determine how patients should be prioritized on the waitlist. While some patients are able to find a suitable living donor, this remains a fraction of the total kidney transplants performed annually (roughly 20%), and therefore is not a focus of this report. However, successful development in deceased-donor kidney transplants would likely result in some utilization of imlifidase in living donor or living donor exchange transplants.

Exhibit 7
Hansa Biopharma AB
Relative Risk of Death Comparing Patients Receiving Deceased Donor Transplant Versus Waitlisted Patients of Dialysis



Source: Wolfe et al., 1999. *New Engl. J. Med.*

Kidney Transplant Allocation Systems

While we do not cover the transplant algorithm for every country or geography in this report, we do provide an overview of the United Network for Organ Sharing (UNOS) in the United States, with a particular focus on the handling and outcomes of patients who are highly sensitized, given the target market for imlifidase. The UNOS is a nonprofit organization that serves as the Organ Procurement and Transplantation Network (OPTN) under a contract with the federal government. All transplant organizations throughout the country are OPTN members and obligated to follow the policies the OPTN creates for allocating organs.

U.S. Kidney Allocation System (KAS). Prior to 2014, a previous version of the KAS allocated kidneys based on specific categories of the recipient, including those patients who needed multi-organ transplants, pediatric patients, patients with zero mismatch, and then geographical proximity. Points were given to patients on the waitlist based on time on the waitlist, donor-recipient human leukocyte antigen (HLA-DR) match, and calculated panel reactive antibody (cPRA) of 80% or greater. This point system clearly biased time on waiting list, given patients were only given a maximum of two points for HLA-DR match and four points for being highly sensitized.

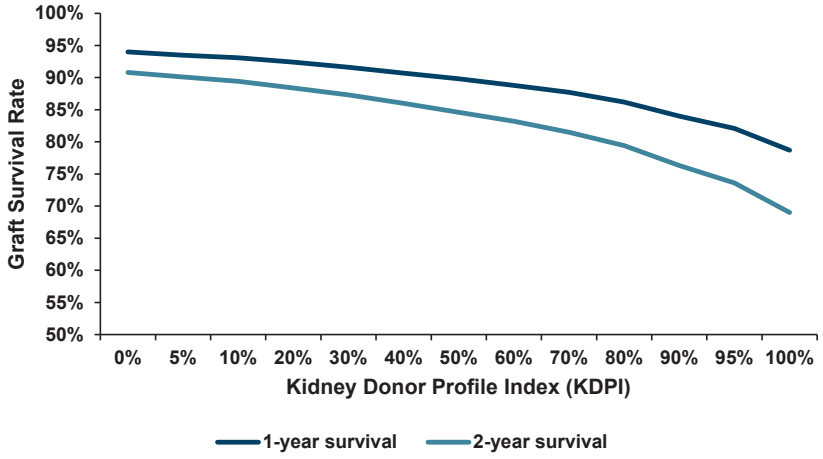
Ultimately, data collected under this KAS showed there were higher-than-necessary discard rates of deceased-donor kidneys, and variability in access to transplants for certain blood types and in certain geographic locations. Therefore, significant work was put into improving the system from the standpoint of improving outcomes for patients, greater utilization of deceased-donor kidneys, and equitable distribution across geographies, age groups, and ethnicities.

In 2014, a new KAS was put into effect, which relied on matching a kidney donor profile index (KDPI) with a recipient's Estimated Post-Transplant Survival (EPTS) score. This is an attempt to match patients with a kidney that may better reflect their expected lifetime. The new KAS was under development for a significant amount of time, and assessed a variety of methods and topics, including age matching, dealing with geographical prioritization, blood types, and sensitization.

The new KAS went into effect in December 2014. Every kidney offered for a transplant has a KDPI score, an assessment of how long the kidney is likely to function when compared to other kidneys, which ranges from 0% to 100%. Lower scores represent kidneys with longer expected survival, with scores of over 85% often considered a cutoff as having lower survival potential. The KDPI score is based on the donor, including age, height, weight, cause of death (such as loss of heart function or loss of brain function), history of high blood pressure, history of diabetes, and serum creatinine.

As shown in exhibit 8, the KDPI score is indicative of the potential graft survival rate of the kidney. Although the relationship is not linear, kidneys with a KDPI of 70% or lower have over an 80% chance of 2-year graft survival, and generally show a linear relationship with KDPI of 0% to 70%. Beyond 80%, the slope of the survival curves is not linear, with a much lower likelihood of 2-year graft survival for higher KDPIs. Given this relationship, kidneys with a KDPI under 35 are typically given priority to younger patients on the waiting list, given the longer potential lifespan of the recipient. In addition, kidneys with a KDPI over 85% were less likely to be donated historically, given the belief they provided worse potential outcomes. With the new KAS, kidneys with a KDPI of 85% or higher are immediately available for regional transplant (as opposed to just local transplant) in hopes of reducing the number of discarded kidneys, particularly if an appropriate patient can be found.

Exhibit 8
Hansa Biopharma AB
Graft Survival Rate by KDPI Profile Index



Source: United Network for Organ Sharing (UNOS) http://optn.transplant.hrsa.gov

Every candidate on the kidney transplant waitlist will also be given an EPTS score. This also ranges from 0% to 100%, to estimate how long the candidate will need a functioning kidney transplant when compared to other candidates. This is calculated based on age, length of time spent on dialysis, whether or not the candidate has received a prior transplant, and the current diagnosis of diabetes.

Highly Sensitized Patients and cPRA Scoring. In humans, major histocompatibility complex (MHC) proteins help differ "self" from "non-self" tissues and proteins, thereby playing a major role in the adaptive immune system. This is the major hurdle for organ transplantation, given the potential for immune-mediated rejection of tissues that do not sufficiently appear to be "self" to the immune system. The extensive polymorphism in the MHC genes, with 1,000 to 5,000 allelic variants across all Class I and Class II genes, can make finding compatible donors that "match" alleles particularly difficult. The MHC genes encode for Class I proteins human leukocyte antigen (HLA)-A, HLA-B, and HLA-C, and the Class II proteins HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, HLA-DRB1, HLA-DRB3, HLA-DRB4, and HLA-DRB5. Class I molecules are expressed on all nucleated cells, and therefore are primary considerations for solid organ transplants, whereas class II molecules are expressed primarily on antigen-presenting cells (such as B cells and dendritic cells) but can be expressed under inflammatory conditions on a variety of cell types including endothelial cells and epithelial cells.

Researchers have developed several methods to evaluate the potential match of HLA alleles between a tissue donor and recipient, and also the level to which a recipient may have preexisting immunity to specific alleles, which are described below. This prior immunity may be due to prior organ transplant, blood transfusion, or exposure to foreign tissue such as in pregnancy.

- *CDC Crossmatch (CDCXM)*. In 1969, Patel and Terasaki published a paper in the *New England Journal of Medicine* detailing patients who had a positive CDC crossmatch with donor lymphocytes had a higher rate of hyperacute rejection and primary graft nonfunction (80% versus 4% for CDC negative). Thus, universal testing for CDC crossmatch began, with a positive test being contraindicated for potential transplantation compatibility. While CDC testing does not have the highest sensitivity given there is typically a threshold of antibody density required for complement activation, it does identify patients who may be at the highest risk of hyperacute rejection.

- *Flow Cytometric Crossmatch (FCXM)*. Newer assays with greater sensitivity have subsequently been developed to test for the presence of donor-specific antibodies. FCXM uses a fluorochrome-conjugated secondary antibody that detects human IgG. Therefore, this assay can detect lower levels of DSAs when patient serum is mixed with donor lymphocytes and can give quantitative levels of antibody via median fluorescence intensity (MFI). While FCXM only detects IgG antibodies, it can detect both anti-HLA and non-HLA DSAs. FCXM can have inconsistencies from individual laboratories due to threshold cutoffs and validation testing. Therefore, FCXM can be tough to standardize across studies or institutions.

- *Virtual Crossmatch With Single Antigen Beads*. Calculated PRA is a computer-based method to test for the presence of antibodies in the patient's serum that may react against HLA antigens from over 12,000 potential donors. More specifically, the presence of specific HLA antibodies, such as to HLA-A2 or B6, are identified in patients by mixing patient serum with beads covered with different HLA molecules. The degree of antibody binding to a specific bead can then be measured and quantitatively assessed as MFI. A computer algorithm then utilizes this information with the known HLAs from over 12,000 historical donors to determine what percentage of future donors would be likely to have the HLA antigens with antibodies present in the patient added to the waitlist. This is therefore a calculated or estimated PRA, although as more historical donors are added to the database the accuracy continues to approve. The use of cPRA was adopted by UNOS in 2007.

  Historically, a PRA could be measured by testing serum from a patient on the waiting list against lymphocytes obtained from a panel of 100 blood donors. The percent PRA is then calculated as the number of lymphocyte samples that react with antibodies from the patient's serum, giving a PRA score of 0% to 100%. This is theoretically used to determine what percentage of potential donated kidneys a person on the waiting list may already have preexisting antibodies against, and subsequently how long they may have to wait for a compatible donor. The cPRA has the benefit of identifying which specific HLA antigens would cause reactivity and screens a much larger pool of potential donor HLA types.

Exhibit 9, on the following page, outlines the benefits and limitations of each method for evaluating DSAs.

Exhibit 9
Hansa Biopharma AB
Methods of Evaluating DSAs

	Single-antigen bead (SAB, virtual crossmatch)	Flow Cytometric Crossmatch (FCXM)	Complement-Dependent Cytotoxicity (CDC) Crossmatch
Timing	When added to waitlist Post-transplant monitoring	At time of transplant	At time of transplant
Class of antibodies detected	IgG	IgG	IgG and IgM
Antigen reactivity (specificity)	Anti-HLA	Anti-HLA Non-HLA	Anti-HLA Non-HLA
Advantages	Highly consistent and large database of HLA	Detects antibodies bound to donor cell surface	Detects antibodies on cell surface capable of CDC activity
Assay sensitivity	Highest sensitivity	High sensitivity	Lowest sensitivity
Drawbacks	Clinical significance of low-level Ab unclear	False positive with poor-quality cells	False positive with poor-quality cells
Interpretation of Results			
High Risk DSAs	+	+	+
Moderate Risk DSAs	+	+	-
Low Risk DSAs	+	-	-
Non-HLA DSAs	-	+	+
Non-IgG DSAs	-	-	+
Low Level Non-HLA DSA	-	+	-

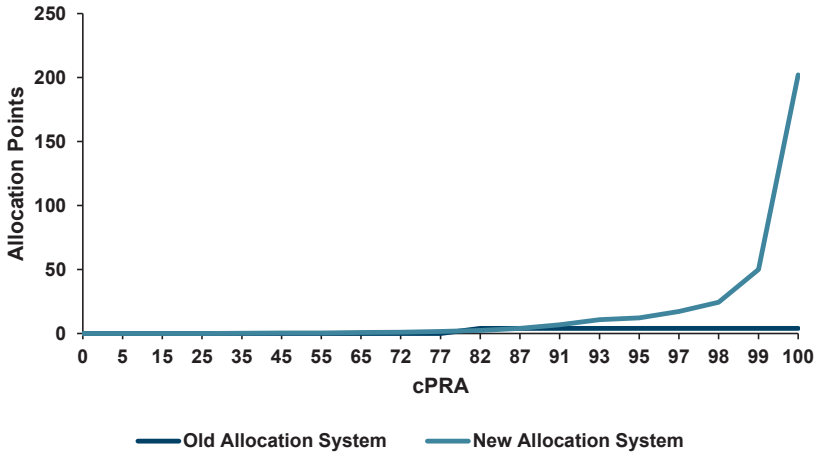
Source: uptodate.com; adapted by William Blair Equity Research

As mentioned, patients who are highly sensitized are given priority under the KAS. Previously, patients with a cPRA of 80% or higher were given four points to influence their standing on the waiting list, but this did not sufficiently prioritize those patients with the highest sensitization (98% or higher) and gave no credit to a patient with a cPRA of 79%. The new system utilizes a sliding scale of cPRA, with patients at 100 getting roughly 200 points, those at 99 getting roughly 50 points, and 98 getting 24 points. Exhibit 10, on the following page, demonstrates the sliding scale for those with a cPRA below 98%.

As many as 15% of all patients on the European transplantation list are highly sensitized, defined as a cPRA of at least 80%, and 8% of patients have a cPRA of 98% to 100%.

Summary of KAS Changes. The changes to the priorities given to patients on the waiting list between the old and new KAS is summarized in exhibit 11 on the following page. We highlight highly sensitized patients, those with a cPRA of 98% or higher, are given first priority under the new KAS regardless of KDPI of the kidney. Importantly, this is not limited to those on the waiting list who are local to the available kidney.

Exhibit 10
Hansa Biopharma AB
Allocation Points by cPRA in Old and New Kidney Allocation Systems



Source: Keith et al., 2016. *Clin. J. Am.Soc. Nephrol.*

Exhibit 11
Hansa Biopharma AB
Kidney Allocation Changes in 2014

Old Deceased Donor Kidney Allocation System(1) (pre 12/4/2014)

SCD (Age<35)	SCD (Age 35+)	DCD (Age<35)	DCD (Age 35+)	ECD	DCD & ECD
0 ABDR mismatch*	0 ABDR mismatch*	0 ABDR mismatch*	0 ABDR mismatch*	0 ABDR	Local 0 ABDR
Local PLDs	Local PLDs	Local PLDs	Local PLDs	Local candidates	Local candidates
Local high CPRA**	Local candidates	Local high CPRA**	Local candidates	Regional	Regional candidates
Local pediatrics	Regional Candidates	Local pediatrics	Regional candidates	National	National candidates
Local adults	National Candidates	Local adults	National candidates		
Regional high CPRA**		Regional high CPRA**			
Regional pediatrics		Regional pediatrics			
Regional adults		Regional adults			
National high CPRA**		National high CPRA**			
National pediatrics		National pediatrics			
National high CPRA**		National high CPRA**			

(1) Candidates were sorted within each classification by total points. Points were awarded for waiting time, CPRA ~ 80%, pediatric, prior living donor, HLA-DR matching. Broad classification groups illustrate the approximate order of candidates in KAS. For full list of classifications, see OPTN Policy 8.
*Includes local, regional, and national distribution. ** Candidates with CPRA at least 80% with a total score higher than the highest scoring candidate with CPRA<80%

New Kidney Allocation System (KAS)(2) (12/4/2014-present)

KDPI 0-20%	KDPI 21-34%	KDPI 35-85%	KDPI 86-100%
CPRA 98-100%*	CPRA 98-100%*	CPRA 98-100%*	CPRA 98-100%*
0 ABDR mismatch (EPTS 0-20%)	0 ABDR mismatch	0 ABDR mismatch	0 ABDR mismatch
Local PLDs	Local PLDs	Local PLDs	Local+ regional A2/A2B-->B
Local pediatrics	Local pediatrics	Local A2/A2B-->B	Local + regional candidates
Local A2/A2B-->B (EPTS 0-20%)	Local A2/ A2B-->B	Local candidates	National A2/ A2B-->B
Local EPTS 0-20%	Local candidates	Regional A2/ A2B-->B	National candidates
0 ABDR mismatch (EPTS 21-100%)	Regional pediatrics	Regional candidates	
Local A2/A2B-->B (EPTS 21-100%)	Regional A2/A2B-->B	National A2/A2B-->B	
Local EPTS 21-100%	Regional candidates	National candidates	
Regional pediatrics	National pediatrics		
Regional A2/A2B-->B (EPTS 0-20%)	National A2/A2B-->B		
Regional A2/A2B-->B (EPTS 21-100%)	National candidates		
Regional EPTS 21-100%			
National pediatrics			
National A2/A2B-->B (EPTS Top 20%)			
National EPTS 0-20%			
National EPTS 21-100%			

(2) Candidates are ordered by allocation points within each classification. Points are awarded for waiting time (back-dated to start of dialysis), CPRA sliding scale, pediatric, prior living donor, HLA-DR. Only waiting time points are used for sorting candidates within each classification for KDPI 86-100% match runs.
Broad classification groups illustrate the approximate order of candidates in KAS. For full list of classifications, see OPTN Policy 8.
*Includes eligible national 100% candidates, eligible regional 99-100% candidates, and local 98-100% candidates.

Source: Wainright et al., 2016. *Am. J. Transplant.*

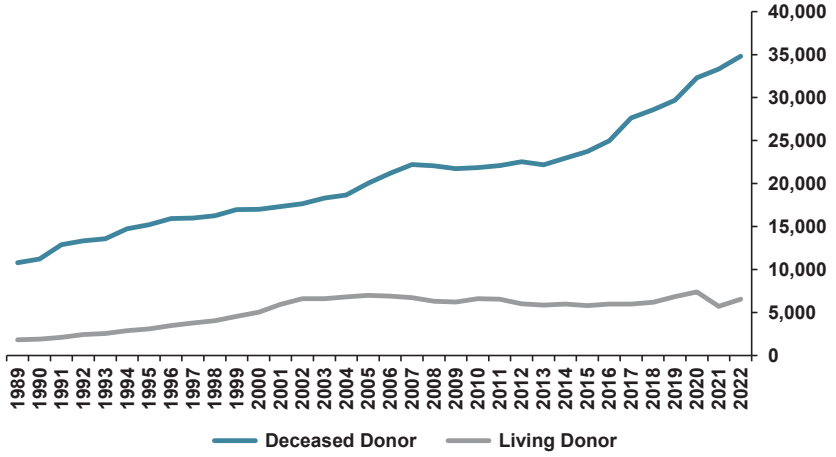
ESOT Guidelines. In the fall of 2022, the European Society of Transplantation published updated guidelines in the journal *Transplant International*, with a focus on handling of patients with HLA antibodies. While the authors do clearly support the use of paired kidney exchange and other prioritization methods to find a matched donor for patients who are highly sensitized, they acknowledge highly sensitized patients—particularly those with a cPRA of 99% or higher—are unlikely to find a suitable matched donor. Therefore, desensitization may be necessary in these patients. The guidelines recommend desensitization strategies start with plasma exchange or immunoadsorption with IVIg or rituximab, but notes that imlifidase is a highly promising new strategy. The guidelines cite the three-year follow-up data from patients transplanted via imlifidase-desensitization, resulting in an 84% death-censored allograft survival.

Ultimately, the updated guidelines from ESOT will impact Eurotransplant, the organization responsible for organ transplant in many European countries including Germany, Austria, the Netherlands, and Belgium. This will allow for imlifidase usage in highly sensitized patients that have spent at least three years in the Eurotransplant Acceptable Programme and is therefore an important step to incorporating imlifidase usage in the protocols for kidney transplantation.

Kidney Transplant Trends

Data in the United States on transplant rates by organ type are available from the OPTN website. As shown in exhibit 12, the annual number of transplants has continued to increase year-over-year, and the rate of increase has accelerated since the change in the KAS in 2014. This growth has come almost exclusively from deceased-donor transplants, as living donor transplants have remained steady at just over 5,000 per year.

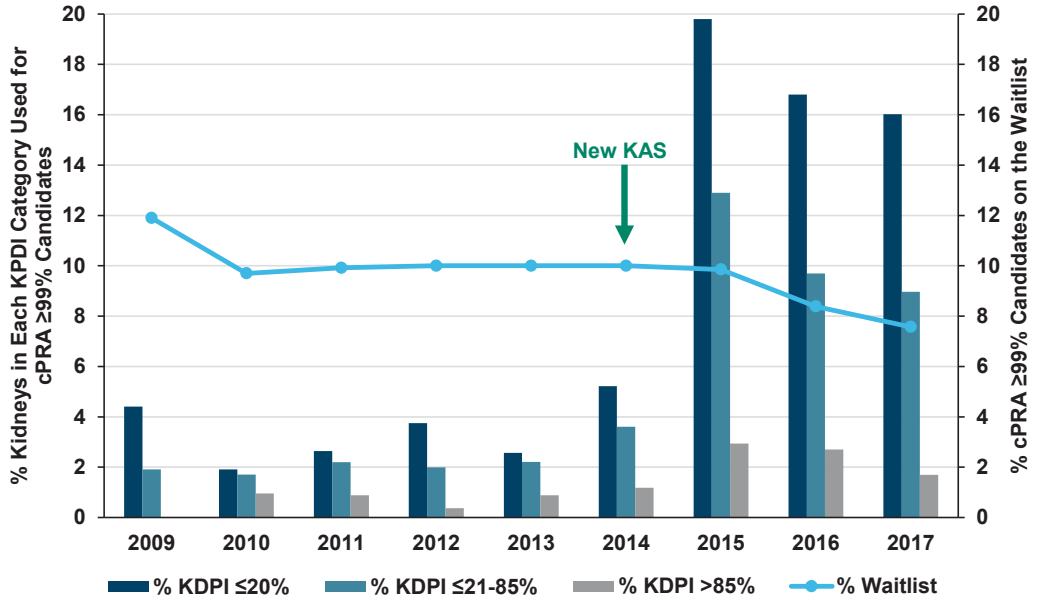
Exhibit 12
Hansa Biopharma AB
Transplants in the United States Over Time



Source: Organ Procurement and Transplantation Network

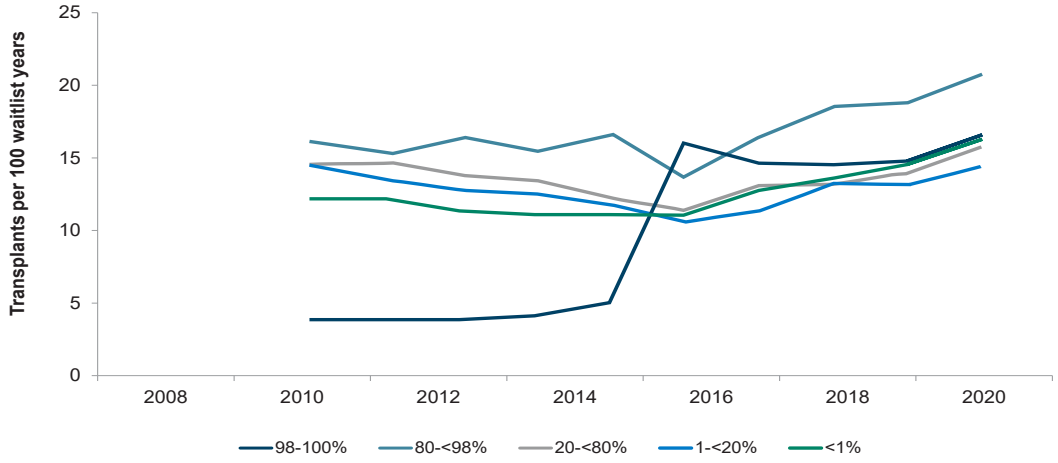
In looking specifically at patients who are highly sensitized (cPRA of 99% or greater), Sethi et al. demonstrated in a 2019 publication the change in the KAS resulted in a significantly higher proportion of kidneys in each KDPI category going to patients who were highly sensitized, and a subsequent decrease in the percentage of patients on the waitlist who were highly sensitized (exhibit 13). Exhibit 14 shows increased donor kidney transplant rates, particularly in patients with high cPRA following the implementation of KAS changes in 2014.

Exhibit 13
Hansa Biopharma AB
Impact of Updated Kidney Allocation System on Transplants in Highly Sensitized Patients



Source: Sethi et al., 2019. *Am. J. Kidney Dis.*

Exhibit 14
Hansa Biopharma AB
Deceased Donor Kidney Transplant Rates by cPRA



Source: OPTN/SRTR 2019 Annual Data Report: Kidney

Despite the successful implementation of the new KAS to increase transplant rates in highly sensitized patients, over 10,000 highly sensitized patients (80% or greater cPRA) are still estimated to be on the waitlist, or roughly 12% of all adults on the waitlist. Looking at higher cutoffs, we estimate 6% to 8% of patients on the U.S. waitlist are at a cPRA of 98% or higher. Hansa estimates roughly 12,000 patients on the U.S. and EU kidney transplant waitlist with a cPRA of 98% or higher, and 5,000 patients with a cPRA of 99.9% or higher.

Overall, the focus on finding compatible kidneys for patients who are highly sensitized has resulted in an increase in highly sensitized patients receiving kidney transplants; however, we continue to believe patients at the highest end of sensitization (99% and higher) will have difficulty finding compatible deceased-donor kidneys. Therefore, the latter group would be candidates for a desensitization therapy that was suitable for the rapid turnaround time of deceased-donor transplantation.

In addition, as the overall rate of kidney transplants increases, we believe more patients will require subsequent kidney transplants, at which point they would be more sensitized due to the prior kidney transplant. This may ultimately increase the need for imlifidase treatment over time.

Imlifidase in Kidney Transplant Desensitization

Phase II Trial of Imlifidase in CKD Patients

Following the healthy volunteer trial described previously, a Phase II trial was conducted in patients with stage V chronic kidney disease (CKD) who were on the waiting list for kidney transplant with at least two identified HLA antibodies, one of which was over 3,000 mean fluorescent intensity (MFI) on single antigen bead analysis. This was a single-center site conducted at Uppsala University Hospital, and although not specifically designed to take patients to transplant, if an eligible kidney donation became available during the trial, patients were allowed to proceed to transplant, and one patient in the trial did successfully receive a transplanted kidney. The results were published in 2018 in the *American Journal of Transplantation* (Lorant et al.).

As was seen in the healthy volunteer study, doses of 0.12 mg/kg and 0.25 mg/kg significantly reduced plasma IgG. Three patients were treated at 0.12 mg/kg, with mean IgG concentrations reducing from 11 g/L at baseline to 0.61 g/L 24 hours after dosing; a 94.5% reduction. These patients were treated with a second dose of 0.12 mg/kg within 32 hours of the first dose, which further reduced plasma IgG to 0.021 g/L; a 99.8% reduction from baseline.

Two patients were treated with two doses of 0.25 mg/kg, and two patients were treated with a single dose of 0.25 mg/kg. All four patients receiving a dose of 0.25 mg/kg achieved over a 99.7% reduction in IgG after 24 hours, and the two patients receiving a second dose at 0.25 mg/kg further reduced IgG levels to a 99.9% reduction from baseline. One patient was given 0.25 mg/kg dose but the infusion was halted after four minutes due to suspected infusion reaction, and although the reaction resolved as soon as the infusion was interrupted, the infusion was not restarted. All patients showed significant reductions in T-cell and B-cell panel reactive antibodies (PRAs) 24 hours after imlifidase treatment.

Although the trial was focused on the safety and pharmacodynamics of imlifidase treatment, patients were allowed to proceed to transplant if a kidney was offered during the study. There was one patient who met the criteria and proceeded to transplant, a 60-year-old man with progressive renal failure and had received a prior kidney transplant. The patient had 13 circulating anti-HLA antibodies with MFI over 500, including HLA-A1, A66, B7, B27, and B47. During infusion with imlifidase, an HLA-B7 kidney was offered, and CDC and FCXM tests were both negative following imlifidase treatment (0.12 mg/kg in two separate infusions).

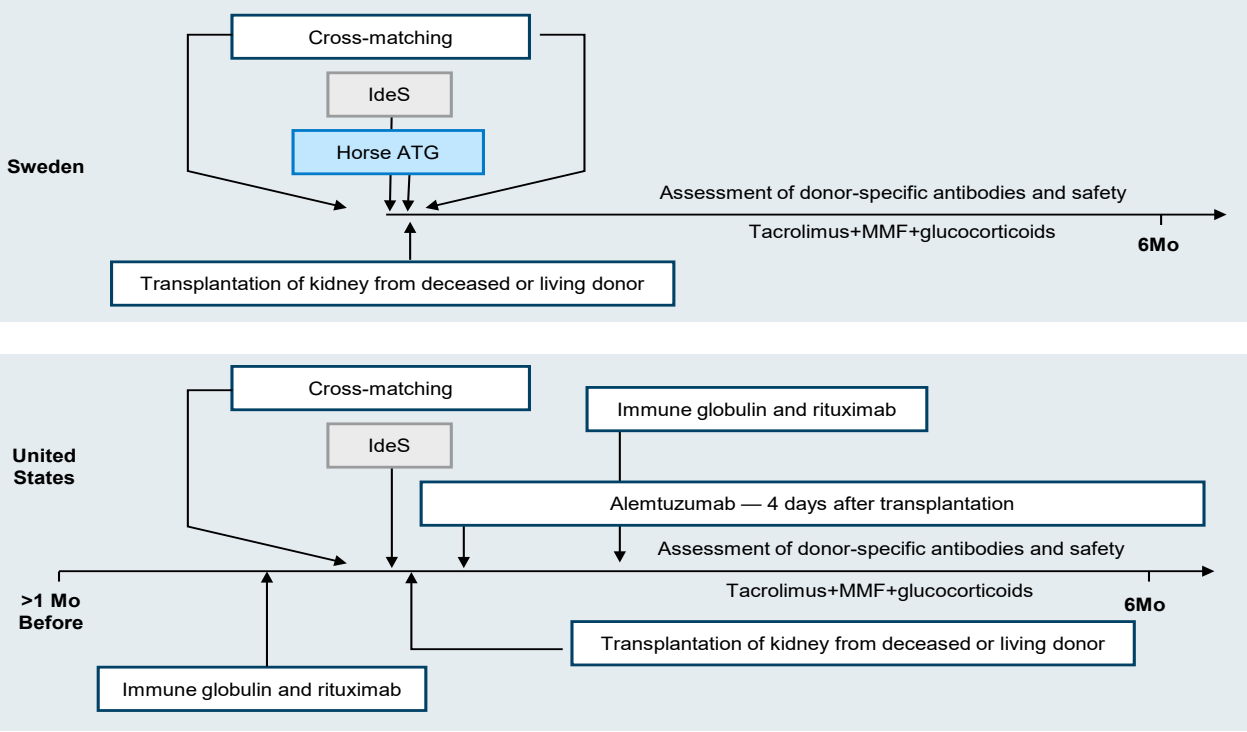
The patient received standard immunosuppressive regimen, and although HLA-B7 antibodies did return, reaching an MFI of 2,700 by month 7 (versus 6,000 pre-transplant), no proteinuria or rejection episodes occurred in the first 36 months of follow-up. This provided a strong proof-of-concept signal for moving imlifidase into Phase II trials in patients waiting for kidney transplants.

Phase II Trials in Highly Sensitized Kidney Transplant Patients

Three separate Phase I/II trials of imlifidase were conducted in patients ahead of kidney transplantation, including two single-center studies and one multicenter study.

The results of two of the single-center studies were published together in the *New England Journal of Medicine* (Jordan et al. 2017. *New Engl. J. Med.*). In 25 patients on dialysis and awaiting transplant who were highly sensitized, imlifidase was given as part of the local center treatment protocol, as summarized in exhibit 15. Patients in the U.S. study had baseline PRA level of 96%, compared to 81% in the Swedish study.

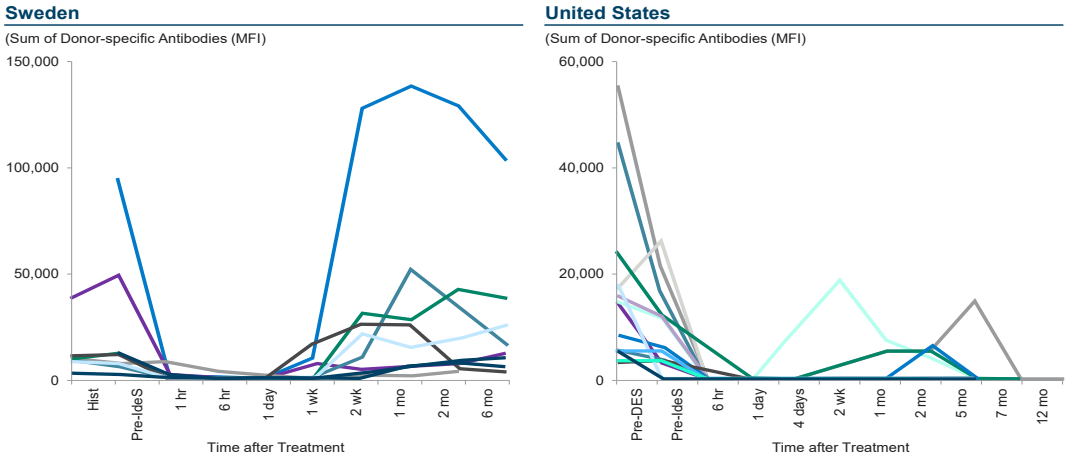
Exhibit 15
Hansa Biopharma AB
Transplant Protocols From Phase II Studies of Idefirix



Source: Joradan et al., 2017. *New Engl. J. Med.*

Imlifidase was administered within four to six hours prior to receipt of the kidney transplant from the incompatible donor. All patients had complete or near-complete reductions in the levels of HLA antibodies and donor-specific antibodies at 6 hours and 24 hours after imlifidase treatment (see exhibit 16). Donor-specific antibodies (DSAs) did show slightly greater rebound by one month in the Swedish study than the U.S. study. The authors believe the difference in anamnestic response was likely due to the difference in the treatment protocols between the two studies, citing the addition of IVIg and rituximab before and after transplantation in the U.S. study.

Exhibit 16
Hansa Biopharma AB
Donor-Specific Antibody Levels in Imlifidase Treated Patients



Lines represent individual patients; image uses estimates of original data
Source: Jordan et al., 2017. *New Engl. J. Med.*

A total of five patients experienced antibody-mediated rejection (AMR), three in the Swedish study and two in the U.S. study. One patient in the U.S. study did experience a hyperacute rejection immediately after revascularization, which was found to be due to IgM and IgA antibodies reactive with donor-allograft endothelium. These antibody subclasses are not cleaved by imlifidase, and therefore would not have been removed prior to transplantation with this treatment protocol.

Overall, the results of these two Phase II studies, although small and uncontrolled, provided strong proof of concept for imlifidase treatment, as part of a broader immunosuppressive regimen, to facilitate kidney transplantation of highly sensitized patients from an incompatible donor.

Highdes Multicenter Phase II Trial. The positive single-center Phase II trial led to a multicenter Phase II study, conducted at five centers across the United States, France, and Sweden. The trial enrolled patients on the kidney transplant waitlist who failed previous attempts at desensitization or were too highly sensitized for available desensitization methods (plasmapheresis and IVIg). All patients were treated with additional immunosuppressive regimens as outlined in exhibit 17.

Exhibit 17
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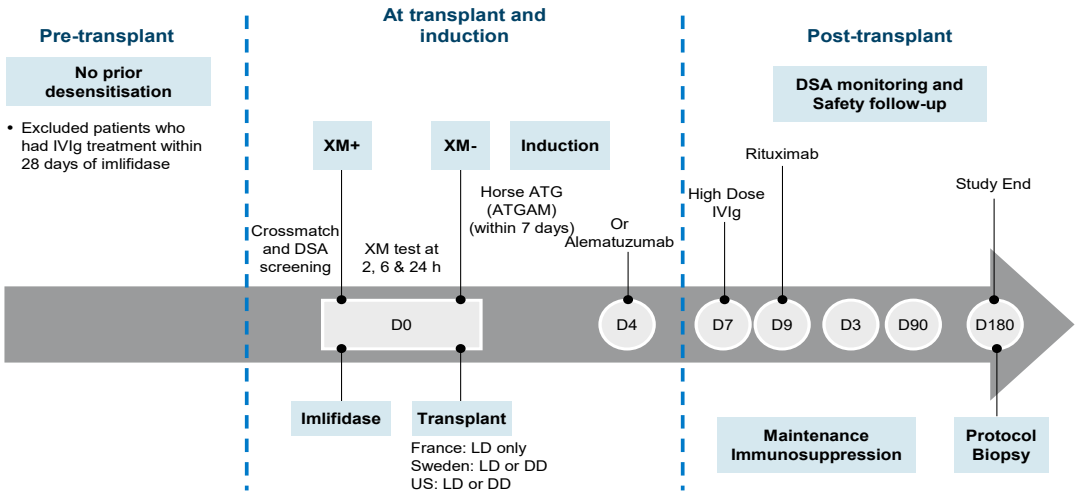
Highdes Trial Design



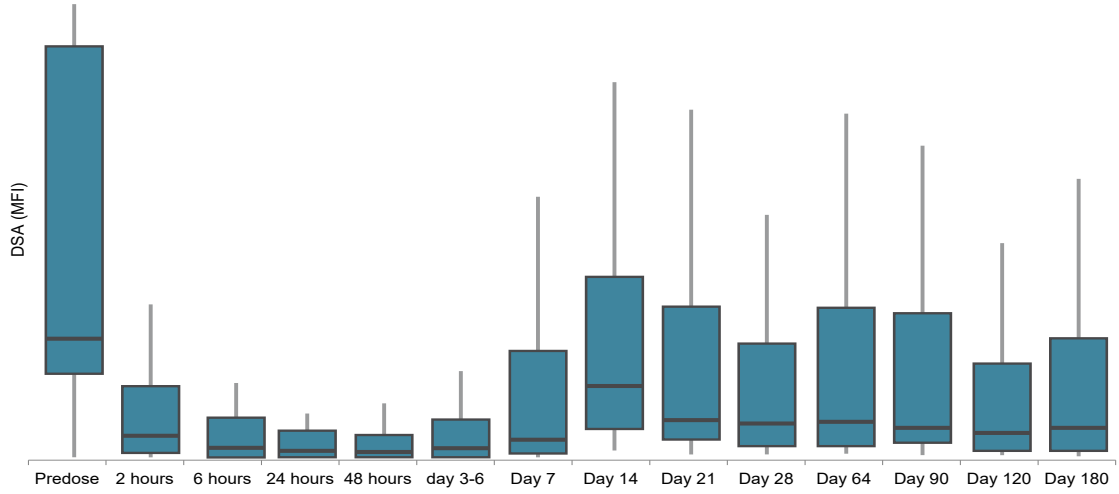
DD = Decreased Donor; DSA = Donor-specific Antibody; IVIg = Intravenous Immunoglobulin; LD = Living Donor

Source: Stanley et al., 2021. *Transplantation*

Nineteen patients were enrolled in the study, but one patient did have an infusion-related reaction, interrupting the treatment after roughly 25% of the dose had been administered and precluding potential kidney transplantation due to lack of IgG cleavage and no conversion of crossmatch. The patients enrolled were highly sensitized, with 90% having received at least one prior kidney transplant and six of the patients having received at least two prior kidney transplants.

After imlifidase treatment, 90% of patients achieved conversion to crossmatch negative within 24 hours. Of the two patients who did not achieve crossmatch negative, one had the infusion stopped early due to an infusion-related reaction as previously mentioned, and a second had a positive crossmatch (FACS, T cell) that was deemed clinically insignificant and did not correlate with the presence of DSAs. Therefore, 18 of the 19 patients received a kidney transplant. The DSA levels are summarized in exhibit 18. As has been seen with other data sets, DSA quickly dropped following imlifidase treatment, but started to return with the production of new antibodies by seven days. However, DSA levels generally stay below pre-imlifidase levels.

Exhibit 18
Hansa Biopharma AB
Donor-Specific Antibodies in the Phase II Highdes Study



Source: Stanley et al., 2021. *Transplantation*

Of the 18 patients who successfully received a kidney transplant, 16 had graft survival at the end of the study (88.9%). Two patients who received deceased-donor kidneys experienced primary allograft nonfunction deemed not secondary to an immune-mediated process. Seven patients (38.9%) had AMR or presumed active AMR, with onset between 2 and 19 days post-transplantation. All AMRs were treated with PLEX, IVIg, optimization of immunosuppressants, and glucocorticoids.

Ten of the 16 patients with successful transplants had biopsies available for evaluation at day 180. Two of the 10 patients did have cg>0, signifying the presence of transplant glomerulopathy, both with chronic-active AMR. One of these two patients had positive C4d and DSA MFI of approximately 9,000, the other was C4d and DSA negative. The results are summarized in exhibit 19.

Exhibit 19
Hansa Biopharma AB
Phase I/II Results With Imlifidase in Highly Sensitized Kidney Transplant

	Highdes	Sweden Study	Cedars-Sinai Medical Center (U.S.) Study
Phase	Phase II (NCT02790437)	Phase II (NCT02475551)	Phase I/II (NCT02426684)
Enrollment Criteria	Patients on kidney transplant waitlist who have failed previous desensitization or whom desensitization is unlikely to be effective Deceased or live donor with positive crossmatch	ESRD on Scandia-transplant Waiting List At least 2 anti-HLA DSAs MFI>3000	ESRD on UNOS Transplant List cPRA>50% DSA and FCMX Positive pre-Imlifidase
Patients Enrolled	19	11	14
Baseline Characteristics	Mean Age: 39.1 Male: 68.4% Previous Kidney Transplant: 89.5% Deceased Donor: 72.2l% Deceased Donor Cold Ischemia Time: 27hr	Mean Age: 52.4±12 Male: 36% Previous Kidney Transplant: 45% Deceased Donor: 82%	Mean Age: 41.4±13.9 Male: 50% Previous Kidney Transplant: 64% Deceased Donor: 100%
Baseline cPRA	99.83 (77.31%-100.0%)	81% (22%-100%)	96% (82%-100%)
Baseline DSA MFI	~6,000	Class I: 4,192 ± 2,372 Class II: 10,464 ± 7,232	Class I: 6,375 ± 1,996 Class II: 6,500 ± 3,571
Additional Treatment Regimen	IVIg + Rituximab, Horse ATG or alemtuzumab, Tacrolimus, MMF, glucocorticoids	Horse ATG, Tacrolimus, MMF, glucocorticoids	IVIg + Rituximab, alemtuzumab, Tacrolimus, MMF, glucocorticoids
DSA Negative After Treatment	89.5%	100%	100%
Percent of Patients Receiving Transplant			
Delayed Graft Function	38.9%	0%	77%
AMR Episode	38.9%	27%	14%
Graft Loss	11% (primary allograft nonfunction)	0%	7% (Hyperacute rejection)
Mean eGFR (ml/min/1.73m^2)	Median: 47	49±13	70±36
Mean Follow-up	At least 6 months	5.7 months	4.0 months
Safety	1 Urinary tract infection probably related	Possibly related infections: 1 blood infection, 1 abdominal infection, 1 catheter-site infection, 1 parvovirus B19 viremia	
Reference	Jordan et al., 2020, *Transplantation*	Jordan et al., 2017 *New Engl. J. Med.*	

ESRD; End-stage renal disease; DSA- Donor Specific Antibody
Source: Source shown in the main body of the table

Conditional Approval in Europe

Hansa first received PRIME (priority medicines) designation from the European Medicines Agency (EMA) in 2017, based on the data available from the Phase II trials, while the Highdes trial was still recruiting patients. At the time, the company believed the Highdes trial, with the additional data available, would potentially support regulatory filings in the U.S. and Europe in late 2018 and early 2019.

In the first quarter of 2019, Hansa officially submitted a marketing authorization application to the EMA, which was accepted in March 2019. During this time, Hansa management had multiple discussions with the FDA on the clinical data available for imlifidase and potential regulatory paths forward. In late 2019, a randomized trial design was initially agreed upon with the FDA to support a BLA filing for imlifidase, which was subsequently initiated in 2021, the ConfIdeS trial.

In June 2020, the Committee for Medicinal Products for Human Use adopted a positive opinion on the review of imlifidase for desensitization of highly sensitized patients needing kidney transplantation. Imlifidase, brand name Idefirix, subsequently received conditional marketing authorization on August 25, 2020. The official indication is for desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased-donor.

Phase III Trial Design in the United States

As mentioned, the Phase III ConfIdeS trial, which has the potential to support regulatory filings in the United States, was initiated in fall 2021, with a goal of enrolling 64 patients. When an organ becomes available and a positive crossmatch is confirmed, patients will be randomized 1:1 to either receive imlifidase or a control arm consisting of remaining on the waitlist or other experimental desensitization treatment (can include plasma exchange, IVIg, CD20 antibody, and eculizumab [Soliris]). The primary endpoint is the estimated glomerular filtration rate (eGFR) at 12 months, and patients who do not undergo transplant or lose their graft will be given an eGFR of zero.

The company announced the first patient was enrolled in December 2021, and as of the company's fourth quarter 2022 earnings presentation on February 2, 2023, 51 of the planned 64 patients had been enrolled. Original plans were to have completed enrollment in the second half of 2022, but that timeline was subsequently modified to the first half of 2023. Following enrollment, management expects to complete randomization in the second half of 2023, but this is event-driven by the availability of donor kidneys. Given the 12-month primary endpoint, the analysis would likely come in the second half of 2024. As of the time of this writing, 13 clinical trial sites were listed as recruiting according to www.clinicaltrials.gov, with management targeting at least 20 centers ultimately.

Based on the Phase II results, we assume 95% of the patients in the imlifidase arm will be converted to crossmatch negative and be able to receive the donor kidney transplant, with 90% of those transplanted having a surviving graft by one year of follow-up. In comparison, we assume hardly any patients in the control arm will receive a kidney transplant during the course of the clinical trial. Given the high level of cPRA required for clinical trial enrollment, the likelihood of finding a crossmatch negative donor is extremely rare. In addition, the high level of cPRA likely makes desensitization using other methods such as plasmapheresis and IVIg extremely difficult, particularly given the time frame needed for deceased-donor kidneys. However, we estimate 10% of patients may receive a transplant in the control arm as a conservative assumption.

Based on the data to date with imlifidase in Phase II trials and other desensitization methods in living donor studies, we assume roughly a third of those patients transplanted will experience delayed graft function or an episode of AMR, which may reduce their eGFR at the final timepoint. In addition, we assume 6% to 8% of patients may potentially lose graft function by the primary endpoint of 12 months, either due to primary graft failure, AMR, or other incident. Assuming patients with successful graft transplants and no complications have an average eGFR of 60 mL/min/1.73m^2, those with delayed graft function or AMR have an average eGFR of 45 mL/min/1.73m^2, and those still on dialysis or with graft failure have an eGFR of zero, our overall assumptions for eGFR in the imlifidase arm is 48 mL/min/1.73m^2, compared to 3 mL/min/1.73m^2 in the control arm.

Confirmatory Trial Design in Europe

As part of the conditional marketing authorization of imlifidase by the EMA, Hansa is required to conduct a post-authorization efficacy study to confirm the clinical benefit in imlifidase, the PAES trial. Hansa announced the first patient was treated in the PAES trial in July, with plans to ultimately enroll 50 highly sensitized patients. The primary endpoint of the trial is one-year graft failure–free survival, where graft failure is defined as dialysis for at least six weeks, re-transplantation, or nephrectomy.

In addition to the patients treated with imlifidase, the trial will also enroll 50 to 100 patients undergoing compatible kidney transplantation at the participating centers to serve as a noncomparative reference cohort. The cohort will not be used for comparison purposes, but will be provided to help contextualize the graft failure–free survival at one year in imlifidase patients.

The clinical trial listing currently includes 10 sites, with three in Spain, two in Sweden, and one each in the United Kingdom, Austria, Belgium, Czechia, and the Netherlands. Management does not plan to provide consistent updates to the PAES trial as far as enrollment progress; however, during the fourth quarter 2022 earnings call in February, the company did say that three patients had been treated and has said the trial needs to be complete by 2025.

Living Donor Phase II Trial

Although deceased-donor kidney transplants represent roughly 80% of all kidney transplants in the United States annually, and therefore is the focus of our report, we believe imlifidase has potential to be utilized in living donor kidney transplantations. A Phase II trial investigating the potential of imlifidase in combination with Velcade, Nulojix, Rituxan, and IVIg in highly sensitized patients with a positive crossmatch toward a living donor was initiated in December 2022 (Clinicaltrials.gov Identifier: NCT05049580).

Patients in the trial will begin treatment with Velcade and Nulojix three weeks prior to transplantation, imlifidase prior to transplantation, Rituxan 8 days after transplantation, and IVIg 10 days after transplantation. The study plans to enroll 12 patients, and the primary endpoint is the proportion of patients who have a rebound in DSA up to three months after transplantation.

While we do not currently include estimates for living donor kidney transplants in our model, we believe positive clinical data would likely result in physician utilization of imlifidase in living donor kidney transplantations in select patients even ahead of any potential labeling extensions. We look forward to the results of the ongoing living donor kidney transplantation trial, expected in 2024, and additional details on next development steps ahead of adding this patient population to our current estimates for imlifidase.

Current Treatment Options

The use of plasma exchange or immunoadsorption, often in combination with IVIg or rituximab, is sometimes capable of reducing DSAs to acceptable levels for transplantation. However, this treatment regimen is inefficient and requires several rounds of treatment to reach acceptable levels.

This creates significant challenges for patients and physicians, particularly in the case of deceased-donor transplantation, considering the organ has to be transplanted within hours of procurement to avoid delayed graft function and allograft loss. In addition, in the case of patients with significant levels of antibodies (as evidenced by large MFI), these strategies may still not be enough to prevent hyperacute reactions post-transplant. We summarize some of the important clinical results and novel therapies currently in clinical development in this section.

***IVIg*.** A randomized trial of IVIg in highly sensitized patients, the NIH IG02 trial, was conducted at 12 transplant centers in the United States from 1997 to 2000. Patients who were highly sensitized with a cutoff of 50% PRA (median baseline PRA of over 80%) were randomized 1:1 to receive either 2 g/kg IVIg monthly for four months with four additional infusions if successfully transplanted or placebo.

A total of 98 patients were enrolled in the study, 48 to IVIg arm and 50 to the placebo arm. During the study, 35% of the IVIg patients and 17% of the placebo patients successfully received kidney transplants in a per-protocol analysis. Of patients who did receive a transplant, 25% in the IVIg group and 38% in the placebo group had graft failure. Acute rejection episodes occurred in 9 of 17 IVIg patients and only 1 of 10 placebo patient. Time to transplant was meaningfully shorter in the IVIg group.

While these results do show some feasibility for IVIg utilization, four months of IVIg therapy only resulted in roughly a 20-percentage-point decrease in PRA levels (IgG down to about 60% PRA at four months), and the PRA levels returned to baseline by month 12. Although not all of the details regarding the immunosuppressive regimen were included in the publication, the low rates of successful transplant and high rates of acute rejection episodes demonstrate limited feasibility from IVIg alone in highly sensitized patients, even when baseline PRA was only 80%.

In a 2013 publication by Vo et al. (Transplantation Journal), 207 patients with cPRA of over 80% were desensitized using the combination of IVIg and rituximab. Of the 207 patients enrolled, 56 had an available living donor and 151 were waiting for deceased-donor kidneys. In all, only 71% of patients were successfully transplanted, 80% of the living donor transplants and 67% of the deceased-donor transplants. Of the patients who received a transplant, 29% experienced an acute rejection (22% antibody mediated) and 5.5% of patients lost their grafts due to antibody-mediated rejections.

In a comparison to matched control patients who stayed on dialysis, the cumulative probability of death was 21% of patients at three years for those on dialysis versus 3.4% mortality rate for those who were desensitized and received a transplant.

Exhibit 20
Hansa Biopharma AB
Clinical Trial Results With Novel Therapies in Highly Sensitized Kidney Transplant

	NIH IG02 Trial		Ninlaro	Benlysta
Phase	-		Phase II (NCT03213158)	Phase II (NCT01025193)
Enrollment Criteria	ESRD on Transplant List cPRA>50%		cPRA≥80% Transplant Waitlist for >24 months	Listed for Kidney Transplant PRA>20%
Patients Enrolled	48 patients	50 patients	10 patients	8 Patients
Baseline Characteristics	Mean Age: 39 Male: 48% Previous Kidney Transplant: 73% Baseline PRA: 80.2%	Mean Age: 42.5 Male: 36% Previous Kidney Transplant: 58% Baseline PRA: 84.6%	Mean age: 40.8 Female: 30% Baseline cPRA≥96%: 70% Previous Kidney Transplant: 70%	Mean age: 41 Female: 75%
Baseline cPRA	PRA: 80.2% ± 2.5%	PRA: 84.6% ± 2.1%	-	-
Additional Treatment Regimen			-	-
DSA Negative After Treatment	IgG PRA Decrease to ~60% by 4 Months	No Change in PRA	20% Decline in cPRA: 0%	No Decreases in DSA
Percent of Patients Receiving Transplant	Per protocol: 35% (16/46)	Per protocol: 17% (8/46)	20%	1/8, considered unrelated to Benlysta therapy
AMR Episode	53%	10%	-	-
Graft Loss	25% (4/16)	38% (3/8)	-	-
Mean eGFR (ml/min/1.73m^2)	Serum Creatinine: 1.68±0.28 mg/dL	Serum Creatinine: 1.28±0.13 mg/dL	-	-
Mean Follow-up	2 years		-	-
Safety	Moderate/severe Headache: 24%	Moderate/severe Headache: 13%	1 thrombotic event, 1 aortic valve disease, 1 hematoma	-
Reference	Jordan et al., 2004 *Journal of the American Society of Nephrology*		www.clinicaltrials.gov NCT03213158	www.clinicaltrials.gov NCT01025193 Study Results

ESRD; End Stage Renal Disease; DSA- Donor Specific Antibody
Source: Source shown in the main body of the table

***Plasmapheresis*.** In a more recent single-center retrospective study, high-dose IVIg, plasmapheresis, and high-dose rituximab were used in 41 highly sensitized patients. The study was collected as part of the Japan Academic Consortium of Kidney Transplantation between 2011 and 2022. The study enrolled 41 patients with positive crossmatch tests (either flow cytometric or complement-dependent). Importantly, the study only included patients with living donors, which we believe exemplifies the amount of time needed to desensitize a patient using plasmapheresis and difficulty in desensitizing a patient in the appropriate time frame of a deceased-donor kidney.

In this study, double-filtration plasmapheresis was initiated roughly two weeks prior to transplant, with three or four sessions conducted every other day. Rituximab was also given roughly two weeks before the transplant, at two separate doses totaling 500 mg. Following plasmapheresis, IVIg was given at 2 mg/kg for patients with positive flow cytometric crossmatch and 4 mg/kg for those with complement-dependent crossmatch. If patients were still crossmatch positive immediately before transplant, a last plasmapheresis session was changed to whole plasma exchange instead of double-filtration.

In addition to this aggressive DSA-reducing regimen, patients also received tacrolimus, MMF, and methylprednisolone starting one month before transplant and continuing post-transplant in a predefined taper regimen.

Thirty-four of the 41 patients underwent graft biopsies, which showed 21 had acute AMR (62%), 14 had acute T-cell–mediated rejection (41%), and 10 had chronic AMR (30%).

The measurement of DSAs was only available in 15 of the 41 patients in the trial. In general, the results show strong decreases in several DSAs across the board (shown in exhibit 21). However, there were many DSAs that were resistant to the protocol, showing MFIs over 3,000 even after the aggressive desensitization protocol.

Exhibit 21
Hansa Biopharma AB
Reductions in Donor-Specific Antibodies With Plasmapheresis

Case	DSA	Pre-desensitization (MFI)	Post-desensitization (MFI)	Last Follow-Up (MFI)
1	BS1	11,186	1,692	0
	BS2	10,808	2,009	0
	DRS1	2,320	0	0
2	DQ6	2,095	0	1,480
3	DR4	11,445	0	3,238
	DR53	20,819	1,252	14,847
	DQ8	20,094	1,942	0
4	A2	13,558	3,602	2,030
5	B35	10,062	2,851	6,345
	DR12	4,414	288	623
6	DR12	19,437	4,327	0
7	A24	13,517	1,832	0
8	DR15	9,016	300	0
9	B44	2,371	0	0
	DR13	4,063	0	4,068
	DQ5	7,169	3,880	0
	DQ6	3,344	5,897	0
10	A24	7,745	0	0
	B7	8,277	0	0
	DR1	6,821	1,824	2,654
11	DQ6	15,656	1,622	0
12	DR7	7,972	0	0
13	DR15	1,710	0	0
14	DR4	1,246	0	0
15	DQ4	8,685	991	0

Source: Ishida et al., 2021. *Exp. Clin. Transplant*

Competition

BCMAxCD3 TCE. Regeneron is evaluating two separate BCMAxCD3 bispecific antibodies (REGN5459 and REGN5458) in patients with chronic kidney disease who are highly sensitized and on the UNOS transplant waiting list. The trial is enrolling patients who have a cPRA of 99.9%, or a cPRA of 98% and have been on the waitlist for at least five years. The primary efficacy endpoint is the reduction of anti-HLA antibodies, and it is unclear if the trial is geared more toward feasibility of transplants from living kidney donors or deceased kidney donors. The clinical trial listing estimates enrollment at 60 patients, with a primary completion date of 2025.

BCMA targeting T-cell engagers (TCEs) are highly potent at depleting plasma cells, as evidenced by the efficacy in multiple myeloma. While this does have the potential to reduce antibody-producing cells, the time from treatment to meaningful reductions in DSAs may be prolonged in vivo given the half-life of IgG antibodies. In addition, continuous treatment with a BCMAxCD3 TCE will likely result in prolonged suppression of IgG antibodies, which may result in greater opportunistic infections, particularly in combination with other immunosuppressive agents used in kidney transplantation.

Kyprolis plus Nulojix. The National Institute of Allergy and Infectious Disease (NIAID) is conducting a Phase I/II trial of proteasome inhibitor Kyprolis (carfilzomib) in combination with T-cell costimulation blocker Nulojix (belatacept) in patients with cPRA of at least 98% who are on the UNOS kidney transplant waiting list. The trial allows for deceased- or living-donor kidney transplants. The efficacy endpoint of the trial is proportion of patients who have elimination of an HLA

antibody or 50% reduction in the MFI of three HLA antibodies at week 20, and successful kidney transplant with a previously incompatible donor without graft loss due to AMR within the first four weeks after transplant. The trial is expected to enroll 15 patients and the estimated primary completion date is in April 2024 (NCT05017545). We note another proteasome inhibitor, Ninlaro, failed to show meaningful changes in patient DSA levels.

Market Model Assumptions

Idefirix received conditional approval from the EMA in 2021 and has recorded sales of SEK 116 million to date. The commercial rollout in Europe has been gated due to the typical staggered reimbursement decisions by country but also the significant education needed for physicians and transplant centers. In addition, given the differences in kidney allocation systems across geographies and transplant protocols by center, significant work must be done to incorporate the potential of Idefirix into these transplant systems and center workflows. Therefore, we are not surprised at the modest level of sales to date, and expect continued commercial expansion, through transplant site and reimbursement decisions, to grow sales over time.

The larger market opportunity is in the United States, given reimbursement potential, key opinion leader influence and experience with imlifidase, and national kidney allocation system. We expect positive clinical results with imlifidase from the ongoing ConfIdeS trial in 2024, resulting in regulatory approval and commercial launch in 2025. While the initial launch in the U.S. may also be gated due to the need to incorporate imlifidase into the KAS and transplant center workflows, we believe the uptake will be faster than that observed in Europe to date.

We believe imlifidase treatment will initially be reserved for patients with cPRA of at least 99.9%, representing around 3% to 4% of all patients currently on the waitlist in the United States and Europe. However, over time we believe physicians will slightly broaden utilization to include some patients with cPRA of 98% to 99.9%, particularly in unique situations or patients who have been on the waitlist for extended periods of time, growing the market opportunity. Lastly, given the continual increase in the number of deceased-donor kidneys, including large numbers in patients under the age of 50, we believe many of these patients will ultimately need a second kidney transplant, and the increased sensitization of these patients will make many eligible for imlifidase treatment.

With a cost at launch of approximately $425,000 in the United States, and a peak penetration of around 20% into the 3,500 patients per year we believe will be eligible for imlifidase treatment in 2035, we derived peak sales of $324 million (SEK 3,375 million) in the United States. In Europe, we model transplant rates in seven geographies (United Kingdom, Germany, Italy, France, Spain, Poland, and Belgium) leading to around 2,000 eligible patients per year in 2035. With a peak penetration into this population of 20%, we derive sales of €113 million (SEK 1,274 million).

Anti-GBM

Anti-GBM Background

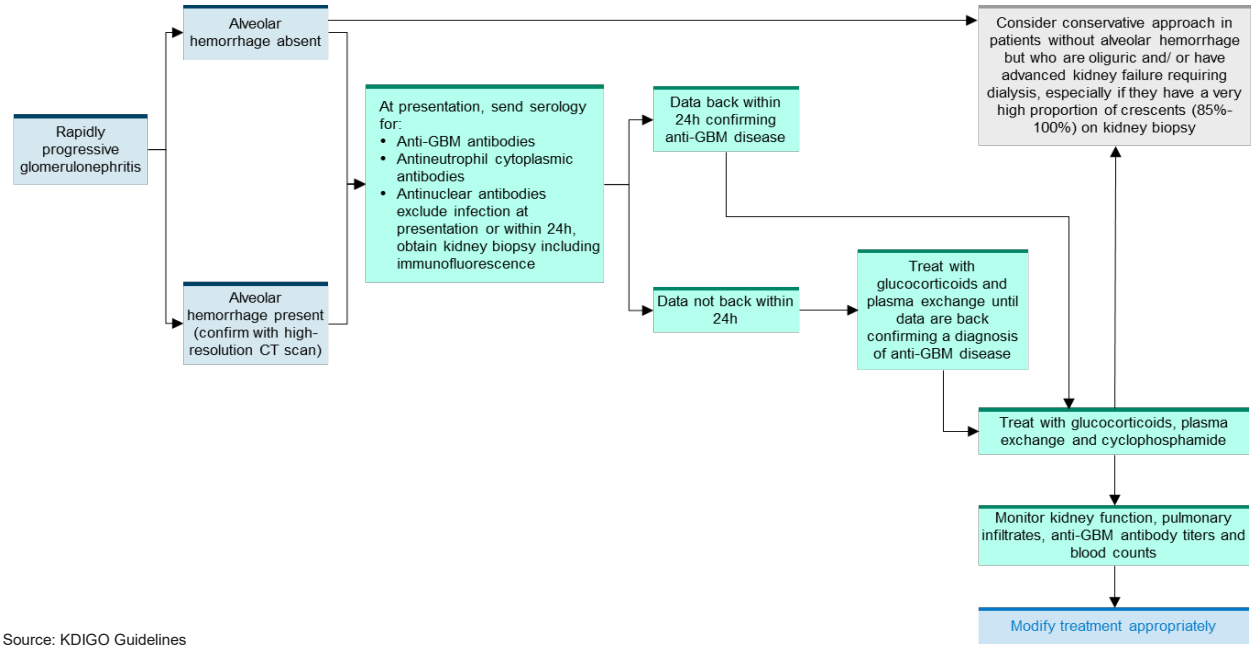
Anti-glomerular basement membrane (anti-GBM) disorder is a rare kidney disease in which antibodies directed against an antigen on the non-collagenous domain of type IV collagen protein present on the GBM leads to acute kidney injury. At diagnosis, around 80% of patients will have crescents in ≥50% of their glomeruli, which is negatively prognostic for renal outcomes with the proportion of crescents observed. In the majority of cases, patients lose kidney function, leading to the requirement for dialysis or transplantation. In 40% to 60% of cases, there can also be lung involvement, with the potential to lead to life-threatening alveolar hemorrhage. The disease is typically monophasic with generally low rates of relapse (0% to 6%; *KDIGO Guidelines*) in patients following the initial pathologic event. Higher rates of relapse have been observed in patients who

co-present with anti-GBM and anti-neutrophil cytoplasmic antibodies (ANCA), with co-presentation thought to occur in about one-third of patients, though these patients also have a greater probability of renal recovery.

The disease can commence with relatively nonspecific symptoms, but the very aggressive inflammatory process that follows can lead to irreparable kidney damage within 2 to 3 weeks. Given the rapidity with which this can occur, the cornerstone of treatment for the disease is rapid removal of the pathogenic antibodies. The disease is rare, with estimates of the incidence of 1.5 per million people annually, suggesting an incidence of around 500 patients per year in the United States.

Anti-GBM has had little by way of clinical development over the last 40 years, with the current standard of care largely defined through clinical experience from treating centers. Current standard of care involves the use of high-dose steroids and cyclophosphamide to prevent continued autoantibody production, followed by numerous cycles of PLEX to remove autoantibodies from the circulation. Work-up and treatment recommendations for anti-GBM from the KDIGO guidelines are shown in exhibit 22. Observational studies have shown PLEX and immunosuppression have decreased early mortality from around 47% to around 9% since its recommended use, and five-year survival is thought to be greater than 90% at present. Five-year renal survival rates have also increased in recent years to around 50% (from around 25%) due to more rapid diagnosis and treatment with PLEX.

Exhibit 22
Hansa Biopharma AB
Anti-GBM Patient Workflow



Source: KDIGO Guidelines

Notably, the KDIGO guidelines do not recommend that patients receiving dialysis at presentation who have 100% crescents or more than 50% global glomerulosclerosis be treated with PLEX and immunosuppression, given the low chance of kidney recovery and risks of intense immunosuppression. With that said, the guidelines do acknowledge that most physicians and patients would likely opt for aggressive treatment given the need for rapid intervention and the consequences of inaction. Guidelines also note that PLEX usually takes 14 days to result in undetectable circulating anti-GBM antibodies, highlighting the need for more rapid-acting agents in the disease. Indeed,

guidelines specifically say: "*As anti-GBM antibodies are pathogenic, they should be removed from circulation as quickly as possible".* The guidelines also recommend initiation of PLEX in the event of a positive anti-GBM antibody test without positive diagnostic biopsy. Other data have suggested a single plasma exchange may remove up to 70% of IgG antibodies, with about five exchanges thought to be required to result in sustained reduction in antibody levels (Dammacco et al., 2013. *Autoimmunity Reviews*).

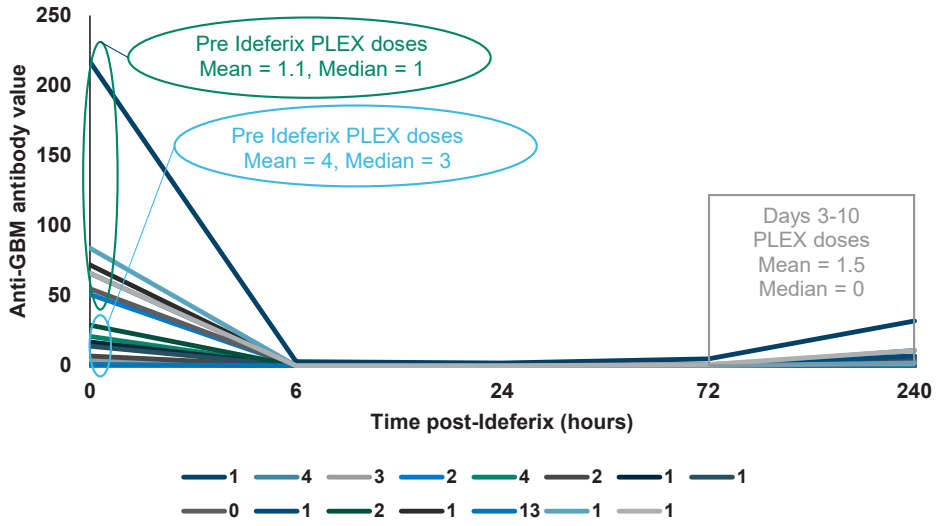
Clinical Data Supporting Imlifidase Use

Clinical data supporting the use of imlifidase in anti-GBM disease comes from an investigator-led, single-arm Phase II study (GOOD-IDES-01) performed in 17 participating European hospitals across five countries. Patients had to have presence of anti-GBM antibodies, eGFR of <15 ml/min/1.73m^2, and could not have been on dialysis for more than 5 days. The study enrolled 15 patients, all of whom received imlifidase at 0.25 mg/kg plus methylprednisolone, cyclophosphamide (daily oral or intermittent pulse), and corticosteroids. Patients also received PLEX a minimum of 36 hours following imlifidase as necessary to keep anti-GBM antibodies below the level of detection in local assays or at levels deemed nontoxic by the investigator.

Among the 15 patients enrolled, 10 patients (67%) were dialysis dependent at the time of enrollment, with five of these patients being anuric. The other 5 patients had eGFR between 7 ml/min/1.73m^2 and 14 ml/min/1.73m^2. Notably, 14 patients had received PLEX prior to initiation of imlifidase with a median of one session, though with up to 13 sessions in one patient.

Six hours post-imlifidase-infusion, all patients had undetectable anti-GBM autoantibodies as shown in exhibit 23. Those with lower anti-GBM antibody levels pre-imlifidase had generally received more PLEX cycles pre-imlifidase than those with higher levels. Rebound in antibodies was observed at day 10 in three patients, though six patients had already restarted PLEX at this timepoint, making it hard to completely attribute the sustained reduction in anti-GBM antibodies to imlifidase. All patients were negative for anti-GBM antibodies at 3 and 6 months post-treatment. Total IgG was also rapidly reduced, though rebounded within 3 to 10 days in most cases.

Exhibit 23
Hansa Biopharma AB
Anti-GBM Antibodies Pre- and Post-Ideferix Treatment



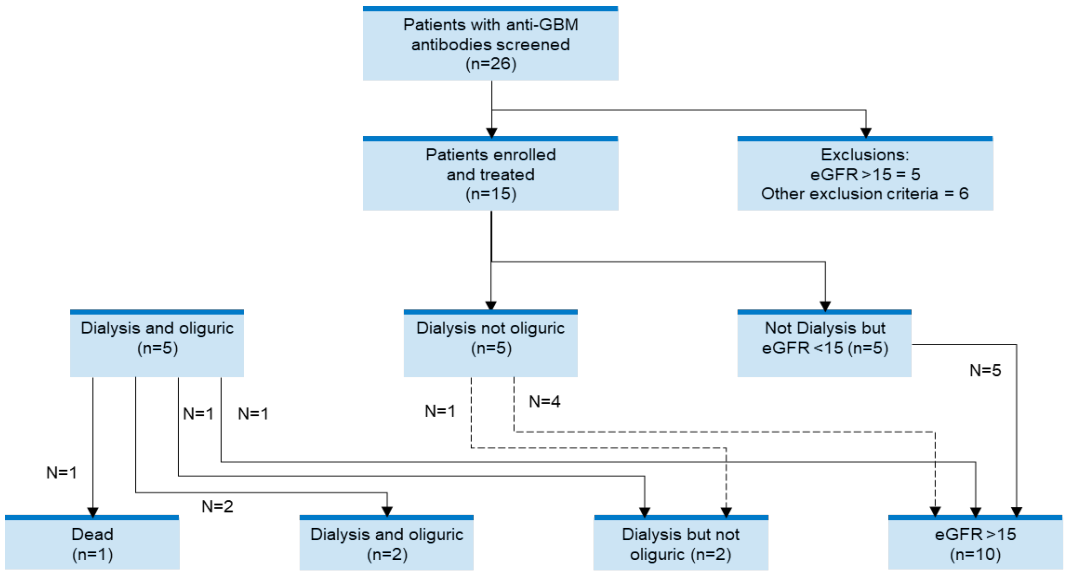
Legend represents the number of PLEX doses received by individual patients

Source: Uhlin et al., 2022. *JASN*.

Over the course of the 6-month follow-up, 10 patients required PLEX resumption due to anti-GBM antibody rebound at a median of 6.5 days post-imlifidase-infusion, with one additional patient receiving PLEX despite no anti-GBM rebound and four requiring no PLEX. Six patients received between 2 and 5 sessions, and four received between 10 and 16 sessions. Daily PLEX for 14 days has been recommended as the initial treatment for patients with anti-GBM (McAdoo et al., 2017. *Clin. J. Am. Soc. Nephrol.*), and thus the use of imlifidase does appear to have reduced PLEX use in the study. All patients received cyclophosphamide with 5 receiving oral therapy, and 10 receiving pulse therapy.

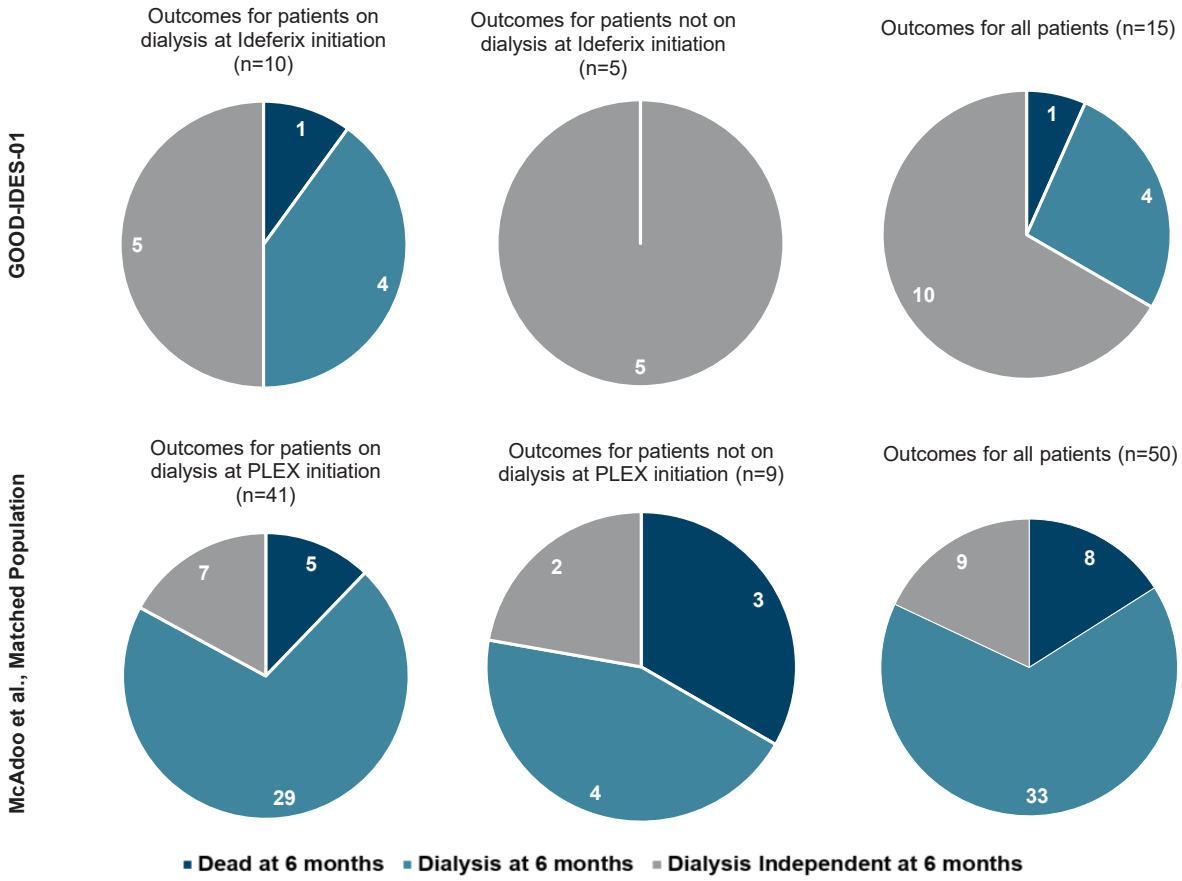
Outcomes for patients are highlighted in exhibit 24 and show 10 patients (67%) were dialysis independent at 6 months. In a letter published in October 2022, it was disclosed that a further patient became dialysis independent at 8 months following treatment with imlifidase, taking the one-year renal survival rate to 73% (Segelmark and Kjellman, 2022. *JASN*). Outcomes from the study were compared to a historical control cohort in which 50 patients who would have met the inclusion criteria for the GOOD-IDES-01 study were evaluated post-hoc. These data are compared to the results from the GOOD-IDES-01 trial in exhibit 25.

Exhibit 24
Hansa Biopharma AB
Patient Disposition in the GOOD-IDES-01 Study of Ideferix in Anti-GBM



Source: Uhlin et al., 2022. *JASN*.

Exhibit 25
Hansa Biopharma AB
Outcomes for Patients With Anti-GBM Treated With Ideferix or PLEX



Source: Uhlin et al., 2022. JASN.

Overall, while caveating with the fact that cross-trial comparisons are less reliable than randomized data, there does look to be clear differences in outcomes. The difference in outcomes reached statistical significance and remained statistically significant when excluding patients with alveolar hemorrhage, which was an exclusion criteria in the GOOD-IDES-01 study (per a requirement of a regulatory body according to management). KDIGO guidelines highlight that recovery of kidney function is only around 5% in patients who are oliguric and/or on dialysis at diagnosis.

Across all 15 patients, eight serious adverse events occurred, though none were considered imlifidase-related. One death did occur at day 58 due to pneumonia in a patient who remained oliguric following treatment. Common AEs included 18 infections that were gastrointestinal or urinary tract in origin, most of which occurred in the first month post-treatment, which is not particularly surprising given the impact on immunoglobulins from imlifidase, PLEX, and other immunosuppressive therapies involved.

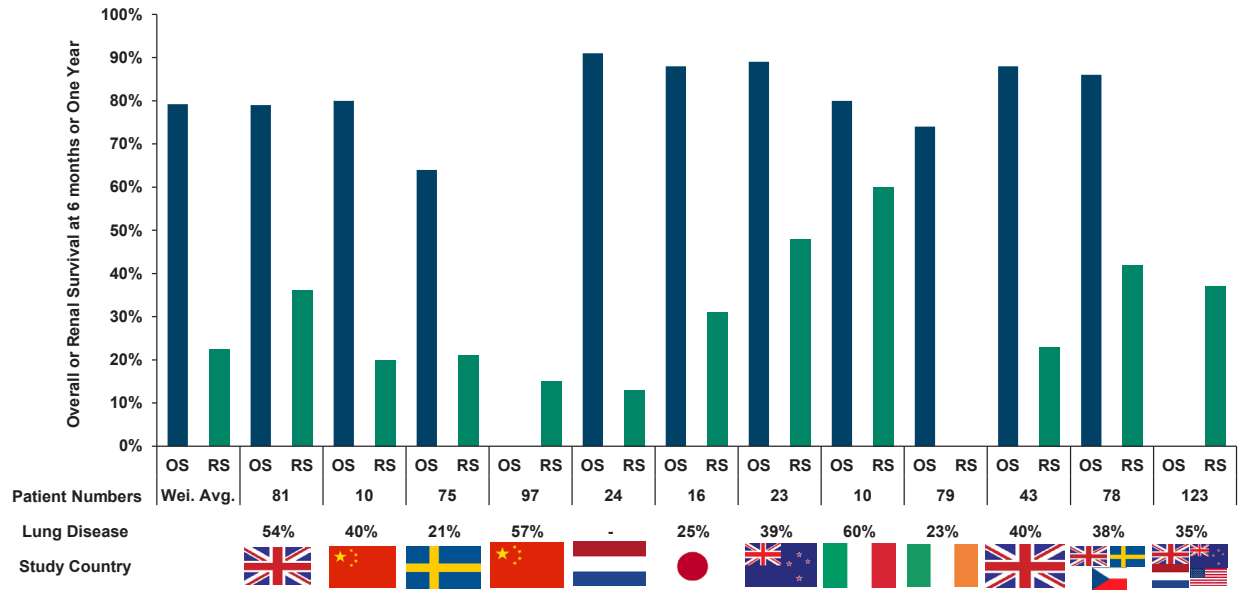
Three patients in the study did not have IgG staining along the GBM, and thus it may be argued these three patients did not have anti-GBM disease. Authors of the study proposed that levels of anti-GBM antibodies may have been undetectable, and that low levels of antibodies, though of unknown consequence in humans, have been shown to enhance toxicity of other autoantibodies in

animal models. However, the specific outcomes in these patients were not reported in results from the GOOD-IDES-01 study, and do make interpretation of the study results a bit more challenging, in our view, given that this makes up one-fifth of the enrollment in the study.

Additional Clinical Data in Anti-GBM

In exhibit 26, we highlight results from several other case series of outcomes at 6 months or 1 year for patients with anti-GBM. Direct comparisons to the results with imlifidase are challenging given the heterogeneity of the patient populations and different timepoints at which results were reported. However, the data highlight low rates of renal survival, with a weighted average renal survival at 6 months or 1 year of 22%. As mentioned, renal survival rates have improved in anti-GBM in recent years and the majority of these are longitudinal studies given the rarity of the disease, thus the renal survival data are likely skewed by data collected over a period of 20 years or more in some cases.

Exhibit 26
Hansa Biopharma AB
Outcomes for Patients With Anti-GBM



Source: Segelmark and Hellmark, 2019. *Nephrol. Dial. Transplant*

One of these studies from a United Kingdom case series highlighted the importance of creatinine concentration at presentation, with those with a concentration less than 500 µmol/L (n=19) having 100% overall survival and 95% renal survival at 1 year. Those with creatinine concentration ≥500 µmol/L but were not on dialysis had a renal survival rate of 83% and an overall survival rate of 82% at one year, while those who were in dialysis-dependent renal failure at presentation had 36% one-year overall survival and 5% one-year renal survival, with no patients becoming dialysis independent (Levy et al., 2001. *Ann. Intern. Med.*).

Another case series from Italy highlighted the poor prognosis of those requiring hemodialysis at initiation of treatment with two of these four patients dying at 6 and 8 months post-diagnosis, and the other two requiring maintenance hemodialysis. The six patients in the case series who did not undergo immediate hemodialysis had progressive renal function improvement and one-year renal survival in all patients (Dammacco et al., 2013. *Autoimmunity Reviews*). However, a retrospective review of data from 43 patients in the United Kingdom with anti-GBM did not find an association between dialysis and mortality, but highlighted oligoanuria (production of less than 100 ml of urine

per day) as the strongest predictor of mortality, with the 16 patients in the cohort who did not have oligoanuria all surviving to one year (Alchi et al., 2015. *Nephrol. Dial. Transplant*). Although dialysis did not predict death in this study, 35 of the 43 patients (81%) were dialysis dependent at presentation, with only two of these patients (5.7%) regaining renal function by one year, and no patients who had oligoanuria recovered renal function. Age, serum creatinine >500 µmol/L at diagnosis, and oligoanuria were all associated with reduced renal survival at 3 months, pointing to important stratification factors for the GOOD-IDES-2 study. Of note in this study, only 32 patients received what would now likely be considered the standard-of-care treatment of PLEX plus cyclophosphamide and steroids. Still, only two of these patients recovered kidney function, and three died in the first year.

Biopsy provides a key insight into the potential to salvage renal function in anti-GBM, with data from on-study biopsies in 123 anti-GBM patients reporting that only one of 15 patients with ≥50% normal glomeruli developed ESRD, whereas no patients with ≥50% sclerotic glomeruli or with 100% cellular crescents recovered from dialysis at presentation (Van Daalen et al., 2018. *Am. J. Clin. Nephrol.*).

Clinical Development Plans

Hansa initiated the Phase III GOOD-IDES-02 study for imlifidase in the fourth quarter of 2022, with the first patient expected to be dosed in the first half of 2023. The open label study is aiming to recruit 50 patients with anti-GBM from 30 to 40 clinics worldwide, who will be randomized 1:1 to either imlifidase plus standard-of-care plasma exchange plus cyclophosphamide and steroid, or standard of care. Unlike the GOOD-IDES-01 study, the GOOD-IDES-02 study will not exclude patients with lung disease, and the eGFR cutoff for enrollment will be <20 ml/min/1.73m^2 compared with <15 ml/min/1.73m^2 in the GOOD-IDES-01 study, potentially providing a patient population with greater chance of renal survival. The primary endpoint will be eGFR at 6 months, and thus should provide a relatively rapid readout once enrollment is complete.

Ultimately, there is consensus in the literature that the sooner that diagnosis and treatment occur for anti-GBM, the better the outcomes, and thus treatment with a therapy like imlifidase with a rapid onset of action in terms of clearing anti-GBM antibodies has strong clinical rationale. However, there is some remaining debate around the benefit of intensive therapy (including PLEX) in patients with very advanced kidney failure, with the likelihood of renal recover very low in patients with serum creatinine ≥600 µmol/L or ≥80% crescent formation (Alchi et al., 2015. *Nephrol. Dial. Transplant*). One small but very outdated prospective study compared PLEX plus immunosuppression to immunosuppression alone, reporting a trend toward improved outcomes in the PLEX group, but those with less severe disease at initiation (<30% crescents and preserved renal function) did well regardless of PLEX use (Johnson et al., 1985. *Medicine*).

Risks to success of the clinical trial likely include enrollment of a high proportion (or imbalance of distribution between arms) of patients with significant renal failure; those already requiring dialysis or with oliguria or anuria. In our view, the benefit of imlifidase treatment in these patients would likely be less given potential for extensive and irreversible damage to the kidneys, though management believes that imlifidase should still be efficacious in these severe patients. Given that preclinical experiments have shown the ability of imlifidase to cleave antibodies already bound to the target antigen/tissue, imlifidase treatment may provide even greater benefit over plasma exchange in patients where there is already humoral-driven inflammation.

One other potential risk identified by Dorin-Bogdan et al. is that the Fab arms of cleaved anti-GBM antibodies that are already bound to the GBM remain attached, creating neoepitopes that may be recognized by anti-hinge antibodies, potentially reinvigorating effector function against the GBM (Dorin-Bogdan et al., 2022. *JASN*). In preliminary studies the authors showed anti-hinge antibodies to be higher in anti-GBM patients than in healthy volunteers. The authors acknowledge these anti-hinge antibodies would also be cleaved by imlifidase upon initial treatment, which we believe

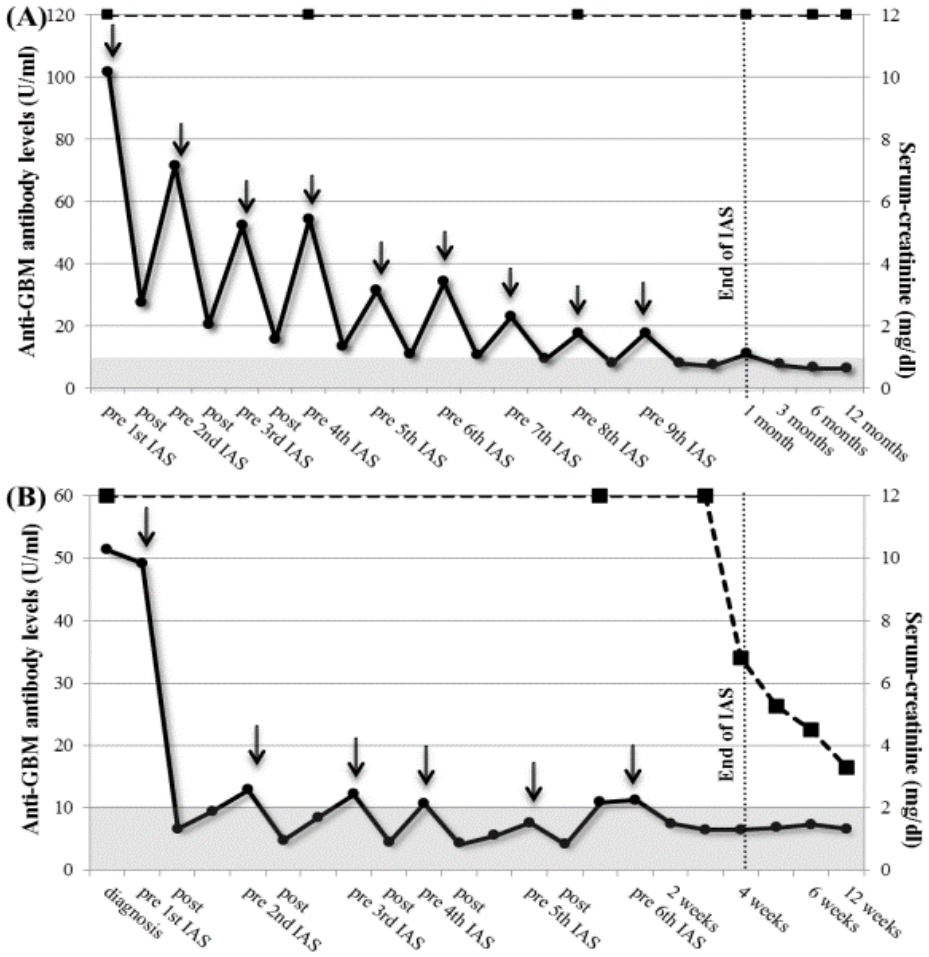
largely negates this potential risk. While the anti-hinge antibodies could return to pre-imlifidase levels within 2-3 weeks, the use of PLEX and steroids will further decrease any clinical impacts combined with dissociation of Fab fragments bound to the GBM in that time frame, in our opinion.

Given PLEX can take up to 14 days to fully remove anti-GBM antibodies from circulation and yet has still been shown to be effective in improving renal survival, we find it hard to imagine cleaved anti-GBM Fab fragments would remain intact on the GBM long enough for anti-hinge antibody recovery to result in a "second insult" and further damage to the kidney. The theoretical concern, however, was one of the reasons for exclusion of patients with lung hemorrhage from the study (Segelmark and Kjellman, 2022. *JASN*), but no evidence of this phenomenon occurred in the GOOD-IDES-01 study in patients with mild lung engagement.

Competition

There is little by way of clinical development ongoing in anti-GBM at present. One single-center study from Austria published in 2015 did look at the potential benefit of immunoadsorption for the treatment of anti-GBM, where dialysis dependency was reversed in three of six patients, and renal survival at one year was 63% (Biesenbach et al., 2014. *PLoS One*). Although these data look positive, the trial reported anti-GBM antibody clearance was about 71% to 86% per treatment, with it taking from two to nine cycles for patients for anti-GBM antibodies to become undetectable with patients receiving an average of 23 treatments (at a cost of around €1,000 per treatment). Kinetics of anti-GBM antibody removal observed in two patients are shown in exhibit 27, highlighting the much slower rate than was observed in the GOOD-IDES-01 study.

Exhibit 27
Hansa Biopharma AB
Anti-GBM Antibody Clearance With Immunoadsorption



Source: Biesenbach et al., 2015. *PLoS One* . Reproduced under the terms of the Creative Commons Attribution License

Market Model Assumptions

Anti-GBM is rare, with an estimated incidence rate of around 1.5 cases per million persons per year. We therefore assume around 500 cases in the United States annually. We assume approval in 2026 and with peak penetration reaching 50% in 2035, we assume around $72 million (SEK 750 million) in peak sales. In Europe, with peak penetration of 40% into our estimate of 800 cases annually in 2035, we derive €90 million (SEK 1,013 million) in sales.

Antibody-Mediated Rejection

AMR Background

Antibody-mediated rejection (AMR) refers generally to the acute rejection of the donor organ, such as a kidney, resulting from a host immune response and often resulting in the destruction of the graft. Rejection episodes can be cellular (lymphocyte driven) and/or humoral driven, with T-cell-driven rejections responding more readily to corticosteroid treatment. Antibody-mediated episodes are characterized by circulating donor-specific anti-HLA (or other non-self, antigen-directed) antibodies generated by B cells and plasma cells, and can be identified through positivity for C4d on peritubular capillaries and various other characteristic histological renal changes. Early signs of an AMR are increases in serum creatinine, decline in kidney function, and well-characterized histopathological features on a kidney biopsy.

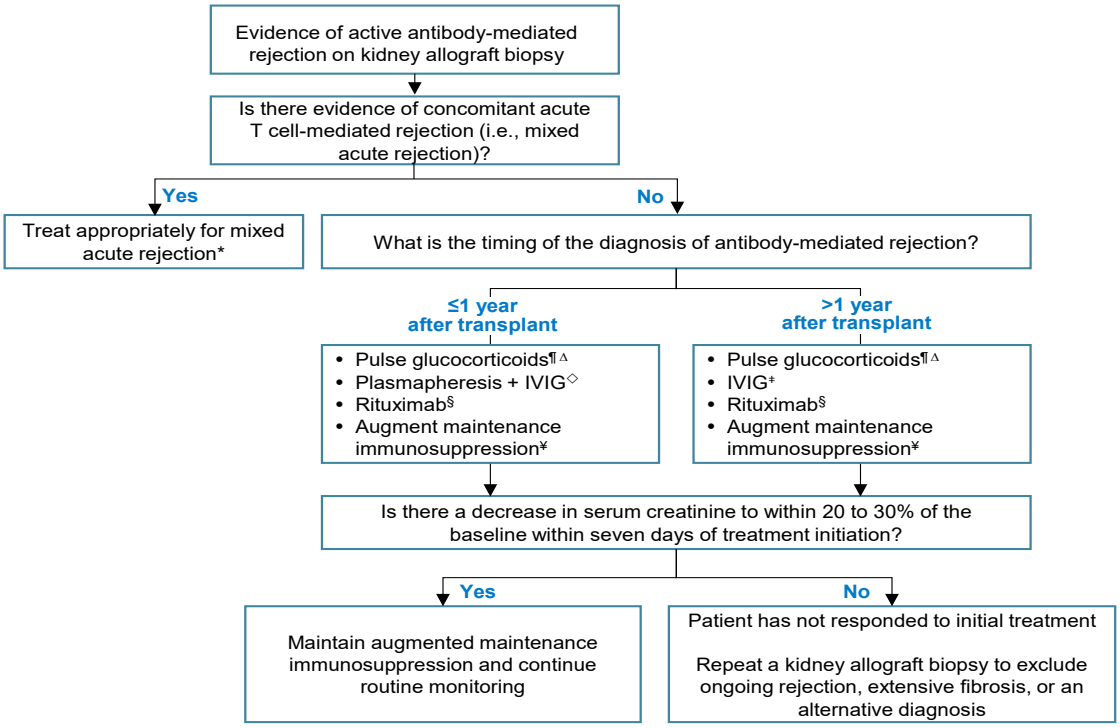
Rejection can be acute (also referred to as active) or chronic. In the active phase, binding of DSAs to the endothelium of the kidneys results in complement-dependent and -independent recruitment of NK cells, neutrophils, and macrophages, all of which contribute to glomerulitis, cellular necrosis, thrombotic microangiopathy, and rapid loss of allograft function. In comparison, chronic AMR arises through the occurrence of a sequence of thrombotic events and associated inflammatory changes eventually leading to allograft injury and remodeling, glomerulopathy, and progressive kidney decline.

AMR has been cited as the most-common cause of immune-mediated allograft loss, and acute AMR has been shown to occur in 5% to 7% of kidney transplants. Some estimates of AMR implication in graft loss are as high as 57% to 63%, indicating that AMR represents a significant challenge for the field. There are numerous factors associated with outcomes, though the graft function at the time of biopsy is a key determinant. Thus, rapidly addressing the cause of graft function loss makes sense as a therapeutic strategy to prevent further rapid decline and increase the probability of saving the allograft.

There are currently no approved therapies for AMR, and KDIGO guidelines note that the optimal treatment approach for acute humoral rejection is yet to be fully determined. Indeed, there have been no large, randomized, controlled trials comparing the safety and efficacy of different therapeutic strategies for AMR. Combination strategies are most often employed to inhibit B-cell maturation and activity, though there is no real consensus on the best means of treating AMR. Patients are most commonly treated with IVIg or plasmapheresis, with other options such as rituximab and anti-T-cell antibodies also being employed.

The goal of treating active AMR is to reduce the titer of DSAs and eradicate the clonal population of cells responsible for their production. In most cases, this consists of a combination of steroids and IVIg, with plasmapheresis and rituximab also being employed in some patients and some recommendations for differential treatment of patients depending on the time since transplant. A suggested treatment algorithm for AMR is shown in exhibit 28. Plasmapheresis daily or every other day is suggested for around six sessions or until serum creatinine returns to within 20% to 30% of baseline, with 100 mg/kg of IVIg being delivered after each plasmapheresis session (to a total target dose of 1,000 mg/kg). Rituximab, if utilized, is usually delivered as a single dose after completion of plasmapheresis and IVIg treatment.

Exhibit 28
Hansa Biopharma AB
Flow Diagram of Patient Treatment Decisions in Antibody-Mediated Rejection



Source: uptodate.com

There have been a number of small clinical trials studying the benefit of plasmapheresis in AMR, with one meta-analysis of five randomized trials of antibody removal showing no significant difference on graft survival (HR: 0.76; Wan et al., 2018. *Transplantation*). However, a sensitivity analysis of three trials with longer follow-up did suggest a benefit for antibody removal (HR: 0.46). Another observational study conducted in France showed that combination treatment with plasmapheresis, IVIg, and rituximab led to 92% graft survival at 36 months versus 50% in patients treated with IVIg alone (Lefaucher et al., 2009. *Am. J. Transplant*). However, a 38-patient randomized, placebo-controlled trial evaluating the addition of rituximab to plasmapheresis, IVIg, and glucocorticoids in patients with active AMR showed no benefit of the addition of rituximab in terms of graft loss or improvement in graft function, with no difference in graft survival at seven years (Bailly et al., 2020. *Transpl. Int.*).

In cases when patients do not respond to initial treatment, immunoadsorption, proteasome inhibitors, IL-6 blockade, complement inhibitors, or even splenectomy may be considered, though evidence supporting their use are of limited quality.

Treatment of chronic AMR is slightly different and is considered more challenging, with allograft damage generally more advanced at the time of diagnosis than in the acute setting. Much like the acute setting though, treatment is ill-defined. Glucocorticoids and IVIg are considered appropriate, as well as rituximab in some cases, though high-quality randomized data is lacking, with therapeutic choices primarily guided by observational data. One single-center study of 123 consecutive patients with chronic AMR followed for a median of 9.5 years post-transplant (4.3 years after chronic AMR diagnosis) reported a 66% reduction in the risk of graft loss in patients treated with IVIg and glucocorticoids (Refield et al., 2016. *Hum. Immunol.*). High DSAs were strongly associated

with higher risk of graft loss (>2,500 MFI; HR: 2.8), and those with surviving grafts had a more significant reduction in DSAs, highlighting the need for reduction in DSAs even in the chronic setting. Another observational study in 78 patients with late AMR (defined as >3 months post-transplant) compared patients treated with steroids and IVIg with or without rituximab. Addition of rituximab resulted in numerically greater reduction in DSAs (despite higher starting levels), greater stabilization of eGFR, and a statistically significant improvement in graft survival (Parajuli et al., 2017. *Transplant Direct*). As with active AMR, there is some evidence for IL-6 blockade, and this is being pursued by CSL Behring in an ongoing Phase III study in chronic AMR with IL-6 antibody clazakizumab (discussed below).

Clinical Data for Imlifidase

The Phase II study enrolled 20 patients with active or chronic AMR who were randomized 2:1 to imlifidase versus 5 to 10 sessions of plasmapheresis (or immunoadsorption at investigator discretion).

In November 2022, Hansa announced the Phase II study met its primary endpoint, showing significantly superior reduction of DSAs in the five days following the start of treatment. Details were limited in the press release, noting only that imlifidase reduced the majority of DSAs in patients with significantly greater degree and rapidity of reduction.

Full data from the Phase II study are expected to read out in the second half of 2023, and Hansa plans to outline additional regulatory plans before the end of 2023. It is unclear at present exactly what the pivotal clinical trial or a regulatory endpoint would look like for the study. The Phase III IMAGINE study of CSL Behring's clazakizumab for chronic AMR (discussed further below) is enrolling 350 patients to a 260-day treatment period. The trial has an interim analysis built in on the first 200 subjects on change from baseline in mean eGFR at week 52, which the company believes should support a conditional approval in the United States in 2025. The final analysis on all 350 patients is event driven on all-cause composite allograft loss and is expected to support global full approval in 2032.

There is little by way of regulatory endpoints outside of hard renal outcomes in the transplant setting. Although the potential for use of DSAs as a surrogate marker has been discussed in prior Banff Kidney Meeting Reports, shortcomings of DSA testing are known to limit its utility as a sole endpoint.

Competition

Much like GBM, there is limited clinical development in AMR at present, though a number of mechanisms of action including complement inhibitors and B-cell–depleting agents have been evaluated. The majority of ongoing development is in the chronic AMR setting, and thus does not address the acute setting where we believe imlifidase would also be efficacious. In addition, given the non-overlapping mechanism of action of other drugs in development, we believe most of these would be considered add-on therapies to imlifidase, rather than alternatives.

Clazakizumab. Clazakizumab is an anti-IL6 monoclonal antibody currently in Phase III development by CSL Behring in AMR. The rationale for evaluating IL-6–targeted therapy in AMR stems from murine studies that suggest IL-6 drives B-cell activation and differentiation to antibody-producing plasma cells. Additional evidence suggests IL-6 may inhibit T regs, which can act to promote immune tolerance of the graft. Last, human studies have suggested elevated levels of IL-6 in serum of patients prior to rejection episodes.

Some evidence for IL-6–targeted therapy stems from use of tocilizumab in the setting of AMR, with one single-arm study reporting 6-year graft survival of 80% and overall survival of 91% (Choi et al., 2017. *Am. J. Transplant*). In a Phase II study in 20 patients with DSAs more than one-year post-transplant, patients were randomized to clazakizumab or placebo for 12 weeks, followed by a 40-week period when all patients received open-label clazakizumab. The study reported treatment

with clazakizumab reduced DSAs to around 75% of baseline (versus no change in placebo-treated patients), with further reduction seen during the open-label extension period (Doberer et al., 2021. *J. Am. Soc Nephrol.*). Proteinuria remained stable on the trial, but eGFR decline was slower in the 12-week randomized portion of the trial in the clazakizumab arm (-0.96 ml/min/1.73m^2 versus -2.43 ml/min/1.73m^2).

The company's Phase III IMAGINE study (NCT03744910) is enrolling patients with HLA DSAs and kidney-biopsy–confirmed chronic-active AMR who are at least 6 months from transplant. The study will enroll 350 patients to either clazakizumab or placebo, with time to allograft loss (defined at eGFR <15 ml/min/1.73m2, return to dialysis, allograft nephrectomy, re-transplantation, or any cause death) as the primary endpoint. Given that the study is enrolling chronic AMR patients, we believe this patient population is distinct from the group Hansa is targeting with imlifidase (particularly given that the control arm is essentially placebo); therefore, we believe there is minimal competitive overlap, and the relatively slow reduction of DSAs seen in Phase II further highlights the rapidity of effect of imlifidase use.

Fostamatinib. Fostamatinib, a spleen tyrosine kinase (SYK) inhibitor approved for the treatment of chronic immune thrombocytopenia, is being evaluated in a Phase II investigator-sponsored trial in chronic AMR (NCT03991780). Preclinical data have suggested a potential role in SYK signaling in autoantibody generation, and in vivo evaluation of fostamatinib in rat models of sensitization using splenocyte transfusion have shown the potential to block the production of circulating IgG and IgM DSAs without impacting total IgG and IgM antibodies in sensitized rats (Tempest-Roe et al., 2022. *Sci. Rep.*). Another study of SYK inhibition in renal transplant showed reductions in allograft damage over time, but did not impact serum DSA levels or the deposition of C4d in the allografts (Chandran et al., 2017. *Transplantation*).

The Phase II study does not define a period of time from transplant, but will enroll 10 patients to up to 52 weeks of fostamatinib treatment. Again, given the focus on chronic disease, the non-overlapping mechanism of action, and the lack of inclusion of the AMR study in Rigel Pharmaceutical's pipeline for the asset, we believe this is unlikely to become significant competition to imlifidase.

Felzartamab. Felzartamab is a CD38-directed antibody designed to deplete the plasma cells believed to drive a number of antibody-mediated diseases. The asset is being developed by HI-Bio in a number of immune-mediated kidney diseases including membranous nephropathy and IgA nephropathy (IgAN). The asset is also being evaluated in an investigator-sponsored trial in AMR (NCT05021484), which was initiated in October 2021 (prior to HI-Bio in-licensing the asset from MorphoSys). Similar to CSL Behring's clinical trial, the study is focused on late- or chronic-active AMR, and is enrolling 20 patients to a randomized, double-blind, placebo-controlled Phase II study of felzartamab versus placebo, with the main focus being safety and PK, though it will also investigate DSAs as a secondary endpoint.

Given that the study requires patients to be at least 180 days post-transplant, and the mechanisms of action of imlifidase and felzartamab are non-overlapping, again we believe the competitive threat from felzartamab, should HI-Bio decide to pursue AMR further, is minimal.

Vyvgart. Earlier this year, argenx added AMR to the list of indications it believes could be addressable with FcRn receptor blocker Vyvgart (efgartigimod). Management is yet to specifically define any plans for development, and this is among 13 indications argenx has outlined as potential market expansion opportunities. Given the main goal of Vyvgart is to essentially replace IVIg use, we believe any clinical study in the setting would likely be designed to replace IVIg and could be beneficial following use of imlifidase to rapidly reduce DSAs initially rather than being an alternative.

Market Model Assumptions
Following the Phase II results, management plans to disclose next steps for the AMR program, but given many regulatory bodies have historically relied on hard renal outcomes in this setting, a meaningful investment may be required for a Phase III study. If endpoints that can be assessed at a fixed time duration, such as change in DSA and eGFR, are not a possibility for registrational trial near term, we believe Hansa may hold off on an official Phase III study, in which case utilization in AMR would likely still occur through off-label utilization following physician comfort gained in the transplant setting.

Our market model for AMR uses the same assumptions for kidney transplantation rates as our market model for imlifidase for desensitization. We exclude patients we assume receive imlifidase for desensitization prior to initial transportation for the eligible AMR population. We assume off-label use of imlifidase beginning in 2026, after approval in highly sensitized kidney transplants in 2026. Although we estimate roughly 1,500 patients per year will experience AMR, we assume imlifidase usage will primarily be focused on the 20% to 25% of patients with severe acute reactions. With peak penetration into this population of 50%, we assume $90 million (SEK 929 million) in peak sales in the United States. Although our assumptions are likely to change as management gains additional information from the Phase II trial and makes determinations of the next steps, our current discounted cash flow analysis for the AMR indication includes a Phase III trial initiating in 2026, with results leading to formal label expansion and increased uptake in the 2030 time frame.

We use the same process in Europe to derive around 1,000 patients eligible for imlifidase in the approval year 2029. With a peak penetration reaching 43% in 2035, we derive peak sales in Europe of €29 million.

Guillain-Barré Syndrome (GBS)

GBS Background
GBS is an acute autoimmune disease affecting the peripheral nervous system that occurs as an aberrant autoimmune response, usually to an infection or other immune stimulation. The immune response then leads to an attack on the myelin sheath or axons of peripheral nerves as a result of cross-reactivity of antibodies to epitopes on the myelin sheath. Pathologically, the disease can present as acute inflammatory demyelinating polyneuropathy (AIDP), which occurs with prominent demyelination, or as acute motor axonal neuropathy, which occurs with prominent axonal loss without T-cell infiltration or complement activation. The cause of disease remains somewhat unknown, though studies have suggested a preceding respiratory tract or gastrointestinal infection can often be a trigger, while some incidences of GBS have been reported following vaccination, though the association risk remains unclear and is thought to be much lower than risk from acute infections.

The disease results in rapid, progressive, often symmetrical weakening in the extremities, and in extreme cases can lead to paralysis or death. This asymmetric weakening in combination with reduced or absent deep tendon reflexes is usually the basis of an initial diagnosis, which is confirmed in the majority of cases with lumbar puncture to confirm abnormal cerebrospinal fluid (CSF) protein levels. The disease is described as monophasic, usually with progression over a two-week period before declining and reaching a low around four weeks post-onset in about 90% of cases. In cases when progression occurs beyond four weeks, usually up to eight weeks, the syndrome is often referred to as subacute inflammatory demyelinating polyradiculoneuropathy, which is managed in a distinct manner to classic GBS. In cases in which progression extends beyond eight weeks, the diagnosis is generally chronic inflammatory demyelinating polyradiculoneuropathy, again with different treatment required.

While full recovery has been reported to occur in about 80% of patients with GBS, 40% of patients can be left with permanent weakening, while mortality has been reported to be as high as 15%. Symptoms of the disease usually begin in the lower limbs, ascending upward and eventually involving the arms and face. Facial palsies and oropharyngeal weakness occur in about 50% of patients with AIDP. Mortality generally occurs as a result of a direct insult on the autonomic nervous system controlling heart rate, blood pressure, and respiration, among other functions. This impact on the autonomic system also leads in some cases to a requirement for ventilation and ICU care in up to 30% of patients.

GBS is thought to occur at an incidence rate of about 1:100,000, with an estimated 10,000 cases per year between the United States, Japan, U.K., Germany, France, Italy, and Spain. One recent study evaluating the prevalence and burden of GBS estimated 150,000 cases globally in 2019, up around 6% since 1990, with around 21,000 cases in high-income North America (Bragazzi et al., 2021. *J. Neuroinflammation*).

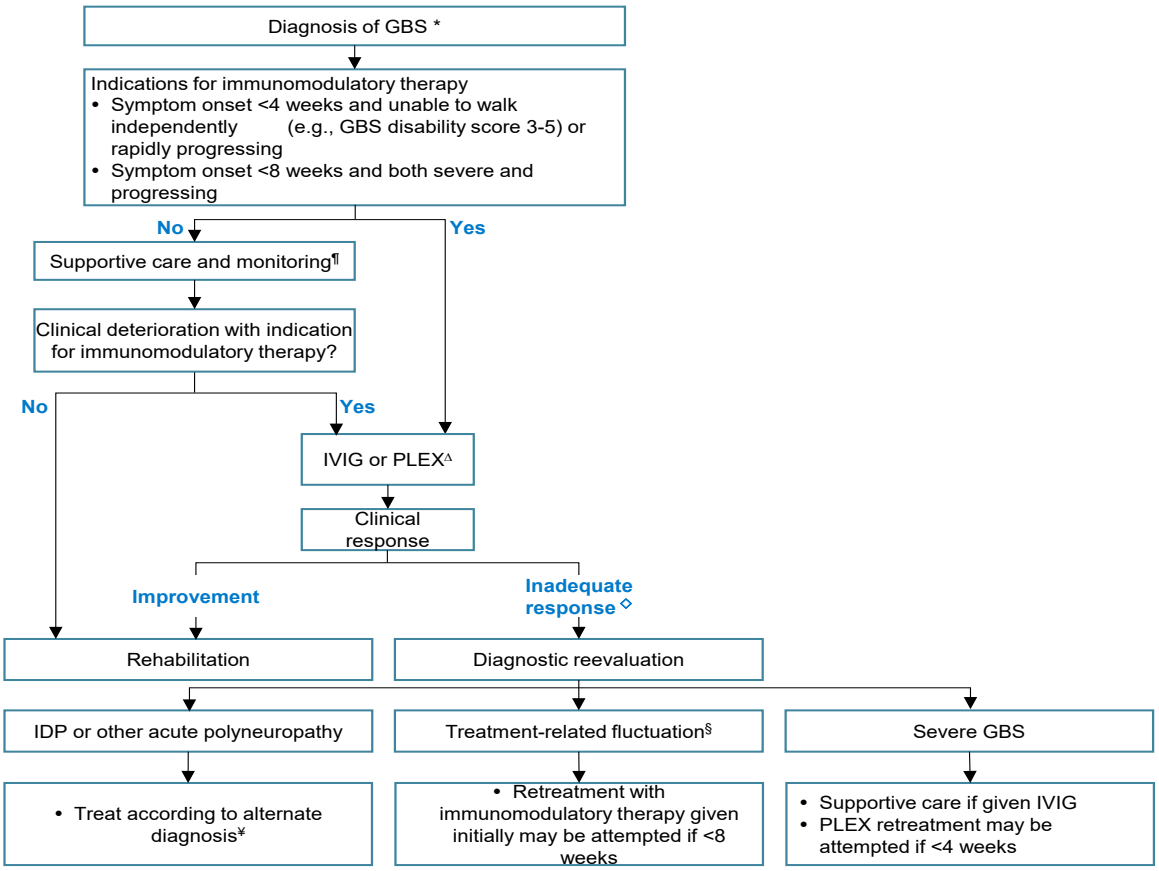
Current Treatment Paradigm

In 2003, the American Academy of Neurology (AAN) published best practice guidelines for the management of GBS, which were reaffirmed in 2022, pointing to the lack of evolution of treatment in the space over the last 20 years.

Treatment with plasma exchange or IVIg forms the cornerstone of treatment of GBS. The AAN recommends plasma exchange in non-ambulant patients within four weeks of treatment onset and in ambulant patients within two weeks of symptom onset, while IVIg is recommended only in non-ambulant patients within two to four weeks of onset, but the effects of either are thought to be equivalent (Hughes et al., 2003. *Special AAN Article*). Notably, corticosteroids are not recommended for the treatment of GBS.

Given the lack of alternative therapies, there are few options for patients with relapsing disease outside of retreatment (no more than one time) with PLEX at two weeks, though retreatment with IVIg is not considered appropriate, and there is limited efficacy data supporting this approach. A suggested current treatment algorithm for GBS is shown in exhibit 29.

Exhibit 29
Hansa Biopharma AB
Treatment Algorithm in GBS



Source: Uptodate.com

Clinical Development Plans

Hansa initiated a Phase II, single-arm, open-label, multicenter study of imlifidase in GBS patients in combination with standard-of-care IVIg. The study did experience some challenges with enrollment during the height of the COVID-19 pandemic, pushing timelines back for the readout from the study. However, the company made changes to simplify the protocol and added sites to expedite enrollment, and announced that the Phase II study was fully enrolled in late-March 2023. A top-line readout remains on track for the second half of 2023, followed by a more comprehensive overview of the clinical data from the trial in 2024. The results in 2024 will include a comparison to an external matched control cohort from the International Guillain-Barre Syndrome Outcome Study database at the Erasmus Medical Center.

Should the Phase II program be successful, Annexon Biosciences' Phase III study for GBS likely provides the best idea of what a Phase III trial design could look like for imlifidase in this indication. The study is enrolling 216 patients to one of two doses of ANX005 (discussed below) or placebo, with a primary endpoint of GBS disability score at week 8. The study initiated in December 2020 and has an estimated completion date of April 2024 according to www.clinicaltrials.gov, and the company expects to complete enrollment in the second half of 2023. The study stratifies patients by their baseline muscle strength and time for treatment onset. In 2023, the company increased the size of its study based on interactions with regulators, but has indicated that improvement

in GBS disability score remains an approvable endpoint, giving the opportunity to demonstrate benefit in patients across the spectrum of the disability scale. Annexon's strategy is actually to replace IVIg in the treatment paradigm (since no randomized studies support its use), and thus the outcome of that trial could provide an important consideration for Hansa if it supports a real shift in the standard of care for the disease.

Competition

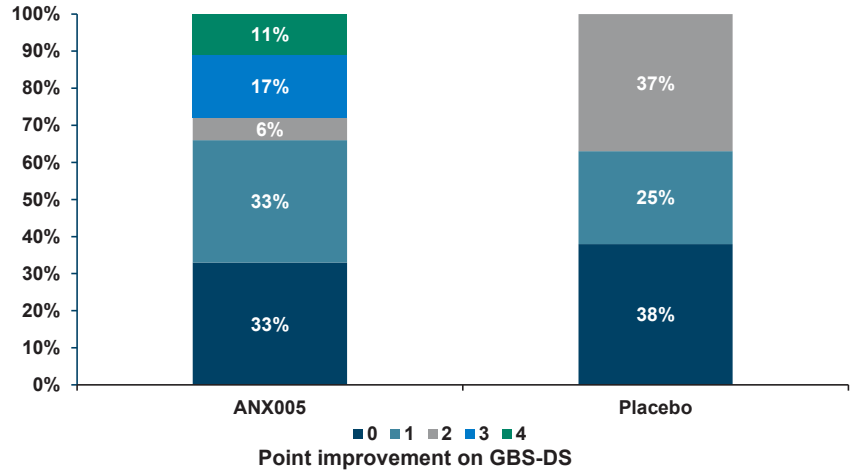
ANX0005. Annexon Biosciences is developing C1q antibody ANX005 in a Phase III study in GBS. C1q, a component of the complement cascade, has been shown to bind pathogenic autoantibodies on nerve cells, leading to complement activation and damage to the axons and nerves in GBS. The asset binds to C1q with high affinity and has been shown to provide complete inhibition of C1q in blood and CSF aiming to block inflammatory processes that result in further damage to nerves. The company has presented data showing significant elevation of complement proteins and fragments in CSF of GBS patients compared to healthy subjects.

Support for Annexon's approach comes from a Phase Ib study in GBS patients enrolled within 10 days of disease onset, in which 38 patients were treated with ascending doses of ANX005 (3 mg/kg to 100 mg/kg) and 12 were treated with placebo. The first five cohorts were treated in a blinded manner for clinical assessment, while two higher-dose groups (75 mg/kg twice and 100 mg/kg) were primarily designed to assess safety and PK. Patients treated were a mean of 7.8 days from initiation of treatment in the ANX005 group, with 77% of patients having a GBS-disability scale score of 4.

PD data were not shown across all doses, though data from a single patient showed complete blockade of serum C1q activity following a single dose of ANX005 at 75 mg/kg. However, a dose-dependent decrease was observed in free C1q in the CSF, with an 18 mg/kg dose seeming to reduce free C1q below the limit of detection. PD data also showed that treatment with ANX005 resulted in a significant reduction in serum NfL (mean 30%), with data from prior studies suggesting serum NfL is inversely correlated with muscle strength and improvement in GBS disability score. There was some evidence of dose-dependent improvements in muscle strength, though these data were highly variable, particularly with only two to six patients in each dose group.

In terms of outcomes, 28% of patients on higher doses of ANX005 (18-75 mg/kg; n=18) achieved a ≥3 point reduction on the GBS disability scale, compared to none in the placebo group (n=8). These data are shown in exhibit 30. Additional data showed that although the same proportion of patients required ventilation on the study, median duration was shorter in the ANX005 group compared to placebo (10 days versus 17 days).

Exhibit 30
Hansa Biopharma AB
Results From Phase Ib Study of ANX005 in GBS



Source: Islam et al., 2020. *AAN*

In terms of safety, no deaths or treatment-related serious adverse events were reported and no discontinuations occurred, though detailed adverse events data were not disclosed.

Additional data were presented in 2021 with preliminary results for the combination of ANX005 and IVIg in 14 patients enrolled in Bangladesh and Denmark, where a single dose of 75 mg/kg of ANX005 was given within the first 3 days of beginning standard treatment with IVIg. Patients had to have a GBS-DS of ≥3 and be within 14 days of symptom onset. Given the symptoms of GBS often begin to decline after 14 days and the uncontrolled nature of the trial, data showing improvement in muscle strength over 8 weeks following treatment are hard to interpret, though PD data showed full target engagement. The data did show that separating patients into two clusters based on Nfl and muscle strength at baseline revealed different recovery trajectories in patients with low muscle strength and high NfL, resulting in slower recovery; though again, subgroups were extremely small.

Unlike Hansa's strategy of combination with IVIg, the company is pursuing a monotherapy indication, and is currently enrolling a 216-patient Phase III study that is expected to complete enrollment in the second half of 2023.

Soliris. Soliris has also been evaluated for GBS, though results for the drug come from a small study run in 13 hospitals in Japan. The study enrolled 34 patients who were randomized 2:1 to a four-week course of IVIg or Soliris (900 mg). Data from the 24-week randomized Phase II study for Soliris were published in 2018, with results showing that at week four post-dosing, 61% of patients could walk independently in the Soliris-treated group, versus 45% in the placebo-treated group.

A Phase III study was conducted and has completed, according to clinicaltrials.gov, though the results of the study have not been reported to our knowledge. The Japan-only study was listed in the Alexion pipeline as of its investor day in September 2022; however, with the company transitioning toward assets with longer patent life (primarily Ultomiris), we believe AstraZeneca is unlikely to pursue a label in GBS, and a Japanese-only study is unlikely to support approval more broadly, in our view. Should additional data prove compelling, there is a possibility that there could be off-label use of Soliris in the setting given the lack of alternative therapies available, though this may see more uptake beyond the patent life of Soliris in 2027 when biosimilars become available.

Market Model Assumptions
We assume an incidence rate of 1 in 100,000 persons annually in the United States, leading to an estimated 3,500 cases annually. We assume approval in 2028, and with a peak penetration of approximately 30% for imlifidase, we derive peak sales of $473 million (SEK 4,919 million) in 2035. In Europe we assume around 7,500 cases annually, and with a peak penetration of 24%, we derived peak sales of €461 million (SEK 5,188 million) in 2035.

Gene Therapy Combinations

The advent gene therapy, or genetically engineering a viral genome to deliver a therapeutically relevant DNA sequence to patients, has sparked significant investment and interest in the biotech field. While significant advances have been made in the development of both ex vivo and in vivo gene therapies, there remain significant hurdles to make these therapies widely available to patients.

One such hurdle for in vivo gene therapies is the presence of neutralizing antibodies to the viral capsid of the gene therapy, either preexisting from prior natural infection or in response to an initial gene therapy administration that precludes re-dosing a patient. This has become particularly true for systemically administered AAV-based gene therapies, given the variable but meaningful percentage of patients with preexisting neutralizing antibodies that would eliminate or significantly blunt viral transduction. While the specific percentage of patients with neutralizing antibodies depends on the serotype of AAV being used and the age of a patient most likely to be treated, the issue has resulted in many companies developing gene therapies to think about how to get the potential benefit of the gene therapy to these patients.

There are key aspects of this situation that are particularly suited to the use of imlifidase. First, the neutralizing antibodies observed against viral capsid proteins are predominantly IgG class. Second, the neutralizing antibodies are highly effective at binding viral capsid in the periphery and blunting transduction, but will not have an impact on the therapeutic payload once translated within transduced cells. Therefore, a one-time treatment with imlifidase has the potential to remove the neutralizing antibodies from circulation, creating a window for gene therapy administration and viral transduction prior to neutralizing antibodies returning.

Preclinical Data
In 2020, researchers from Spark Therapeutics evaluated the potential of imlifidase to increase tissue transduction of engineered AAV vectors in the presence of neutralizing antibodies. In models of AAV8 transduction, mice were transfused with neutralizing amounts of IVIg and then treated with imlifidase or placebo prior to administration of an AAV8 vector expressing luciferase. Luciferase expression levels in animals receiving imlifidase were in the range of control animals who did not receive IVIg. In contrast, animals who received IVIg and then vehicle control treatment showed no luciferase expression.

Evaluation of vector copy number in hepatocytes did show lower levels in IVIg plus imlifidase–treated animals than in those who received phosphate buffered saline plus imlifidase, showing there was still some level of neutralization present after imlifidase treatment, which may have been due to antibody fragments or residual IgG not detected by neutralization assays.

The paper also describes a preclinical model with human factor IX in mice and nonhuman primates, both cases of which show the ability of imlifidase treatment to remove neutralizing antibodies and facilitate greater AAV8 transduction. In the NHPs, both monkeys pretreated with imlifidase showed higher levels of vector company numbers and human factor IX transgene expression. Interestingly, the NHPs treated with imlifidase also exhibited lower, or more transient, anti-AAV8 antibodies following systemic AAV8 administration.

The study also evaluated the potential to use imlifidase in an AAV-vector re-administration setting. In this experiment, one NHP was given imlifidase and one placebo prior to systemic AAV8 exposure. Both animals developed anti-AAV8 IgG in response to AAV8 exposure, although the imlifidase-treated animal developed significantly lower anti-AAV8 levels. At day 82, both animals received two doses of IdeS, which reduced anti-AAV8 IgG. AAV8 vector was then re-administered to both animals. The NHP that had received imlifidase prior to each AAV8 infusion had higher vector copy number and continued to show less anti-AAV8 IgG than the control NHP.

The last in vivo experiment evaluated eight NHPs immunized with AAV-LK03, and then randomized at day 210 to PBS or imlifidase treatment prior to retreatment with AAV-LK03. The five NHPs that received imlifidase saw a significant decrease of anti-AAV-LK03 antibodies, and subsequently had significantly higher expression of the human factor VIII transgene in the AAV vector.

Importantly, the study also noted imlifidase cleavage of IgG antibodies was more efficient ex vivo with human plasma than what was observed with NHPs, where residual scIgG was observed.

In 2022, a study evaluating IdeS in a mouse model of mucopolysaccharidoses (MPS) IIIA gene therapy was published by researchers at the University of North Carolina at Chapel Hill (Bobo et al., 2022 *Gene Therapy*). In this model, rabbit anti-AAV9 IgG was generated by immunizing rabbits with a recombinant AAV9 viral vector, and then collecting the rabbit serum and purifying total IgG. Mice were then infused with the rabbit total IgG prior to being treated with IdeS and systemically delivered AAV9 viral vector.

As would be expected, IdeS treatment rapidly reduced IgG levels, including anti-AAV9. This resulted in no significant difference in the tissue vector copies between IdeS-treated MPSIIIa mice and control mice that did not receive the rabbit anti-AAV9 IgG. In contrast, the anti-AAV9 IgG was able to significantly lower tissue vector levels in the liver, brain, lung, and intestine in vehicle control mice.

Ongoing Clinical Collaborations

***Sarepta*.** In September 2020, Hansa and Sarepta Therapeutics announced a collaboration to develop and promote imlifidase as a pretreatment for gene therapy in Duchenne and limb-girdle muscular dystrophy patients who have preexisting antibodies to AAV.

Sarepta is currently under regulatory review for the company's novel gene therapy, SRP-9001, which utilizes the AAVrh74 vector to deliver a micro-dystrophin gene to patients with DMD. An estimated 14% of DMD patients have preexisting IgG antibodies to the rh74 vector, and the companies plan to begin a clinical trial evaluating imlifidase pretreatment in 2023.

Although the preclinical data for this specific combination has not been disclosed, we anticipate the results will likely be presented at a medical conference this year in support of the clinical trial initiation. The press release in November 2022 announcing the plans to initiate a clinical study evaluating the combination did note the preclinical data results demonstrated the feasibility of imlifidase to reduce preexisting IgG antibodies to rAAVrh74, and we therefore look forward to additional disclosures of this preclinical data.

Hansa is eligible to receive just under $400 million in development, regulatory, and sales milestone payments, in addition to booking all sales of imlifidase and tiered royalties up to the midteens on incremental gene therapy sales in patients with preexisting antibodies.

AskBio. In January of 2022, Hansa Biopharma enter into an agreement with Asklepios BioPharmaceutical (AskBio), a wholly owned subsidiary of Bayer AG, to evaluate the potential of imlifidase prior to AskBio's gene therapy in Pompe disease. AskBio is responsible for conducting all research under the terms of the agreement and will have an exclusive option to enter into full development and commercialization following the initial feasibility studies.

Competition

IdeXork. Selecta Biosciences is developing IdeXork (Xork), a proprietary IgG protease, that the company says has the ability to cleave human IgG. Although the company has released limited information regarding the Xork program, the company has disclosed it is derived from a nonhuman pathogen and believes there is less preexisting humoral immunity to Xork than IdeS. In one preclinical experiment, the company has shown around sixfold lower anti-IgG protease antibodies in human serum for Xork compared to IdeS.

The company announced a clinical trial collaboration with Astellas Gene Therapies in 2023 for use with AT845, a gene therapy for Pompe disease. Under the agreement, Selecta received $10 million upfront payment and is eligible to receive $340 million in development and commercial milestones plus royalties on any potential commercial sales where Xork is used as a pretreatment for AT845.

Market Model Assumptions

Given the stage of development with the company's two announced collaborations, we do not include estimates for the Sarepta program in DMD at this time. The FDA is currently reviewing SRP-9001 for patients with DMD, although we do not assume the initial approval will lead to utilization in patients with preexisting rAAVrh79 antibodies. However, successful clinical data demonstrating comparable transduction with imlifidase pretreatment versus those without preexisting antibodies should allow for a rapid development path, assuming SRP-9001 continues to demonstrate clinical benefit in ongoing trials.

Although the current cutoff for preexisting AAVrh79 antibodies would suggest 14% of patients would be eligible for treatment with imlifidase, we believe there is potential to utilize imlifidase in patients with lower antibody titers to help ensure sufficient transduction, and longer-term potential to use imlifidase to retreat those patients who were previously treated with SRP-9001 and develop anti-AAVrh79 antibodies. Therefore, the use-case for imlifidase may ultimately grow beyond an initial 14% of the 3,300 addressable patients diagnosed annually with DMD.

In addition, successful development in DMD should result in accelerated development of imlifidase in limb-girdle muscular dystrophy.

NiceR

The development of imlifidase has potential across many disease indications driven by IgG immunity; however, its utilization is limited by an anti-imlifidase immune response generated in humans. This immune response to imlifidase has the potential to neutralize activity of subsequent infusions and also increases the risk for an anaphylactic reaction in response. For nearly a decade, Hansa has been working on improving imlifidase with a second-generation IdeS molecule capable of being given repeatedly without the anti-IdeS immune response.

In general, reducing the immunogenicity of proteins is accomplished by altering or hiding amino acid sequences found to be immunogenic. A variety of methods have been utilized historically to reduce immunogenicity, with varying levels of success, such as PEGylation of proteins to "mask" the immunogenic segments from immune recognition and single amino acid changes to disrupt B-cell epitopes. There are many difficulties in making these changes to therapeutic proteins, including preserving the function of the protein and difficulty in predicting which sequences may become immunogenic following changes in the amino acid sequence.

Although minimal details have been disclosed by Hansa to date, we believe the company has focused on removing the B-cell epitopes that have been shown to generate humoral responses in the extensive clinical experience with imlifidase.

HNSA-5487
On Hansa's fourth-quarter earnings call in February 2023, the company disclosed IND-enabling toxicology studies for lead NiceR program HNSA-5487 were completed in the end of 2022, setting up for a potential IND submission and clinical trial initiation in 2023. Management has not disclosed meaningful details on the NiceR program to date, but we are hopeful now that clinical trials are set to initiate, additional preclinical data can be disclosed for the molecule.

We expect an initial dose escalation, both single-ascending and multiple-ascending doses of HNSA-5487, will be designed to examine the extent of IgG reduction and immunogenicity in healthy volunteers. Given the efficacy of imlifidase, we believe positive data from the healthy volunteer study showing comparable IgG reductions and minimal humoral response would be a strong proof-of-concept signal and a major inflection point for the program.

Minimal humoral response to HNSA-5487 in healthy volunteers would be a significant positive for the program, but we believe it is important to acknowledge that a humoral response in healthy volunteers may not be equivalent to the response in patients with autoimmune disease on background immunosuppressive therapies. These immunosuppressive regimens may further blunt a humoral immune response, therefore allowing re-dosing even if it is precluded in healthy volunteers.

Hansa has not disclosed development plans for HNSA-5487, only saying there are potential opportunities in autoimmune diseases, transplant settings, or oncology. The potential in de-sensitizing patients prior to hematopoietic stem cell transplants does appear to be an indication of interest for Hansa, but clearly initial data from the healthy volunteer data will be essential in determining the best path forward.

Intellectual Property

The company's lead product, imlifidase, is protected by six patent families including both granted patents and pending applications for methods of use of imlifidase. The company's IP portfolio of patent families related to imlifidase and its use has a coverage span until 2035 in key markets including the U.S., Europe, and Japan. Patents with expirations up to 2035 can be extended up to five years via available patent term extensions.

In addition, Hansa continues to explore additional exclusivity protection for its products stemming from orphan drug designations and other data exclusivity periods. Since 2017, Hansa has been granted five orphan drug designations by EMA and the FDA across transplantation, anti-GBM disease, and GBS (only FDA). Orphan drug designation provides development and commercial incentives, including 10 years of market exclusivity in the EU and 7 years in the United States.

Risk Factors

Risk factors for Hansa can be classified into major areas of technical and clinical, regulatory, commercial, and competitive risks. In general, however, the risk exposures are similar to other biotechnology companies in early stages of commercial launch with ongoing clinical trials, but the level of risk and time frame in the categories mentioned may vary from that of peers.

Technical and Clinical Risk
Like most biotechnology companies, Hansa has risk of clinical setbacks, which is heightened by the fact that the company's pipeline is built around a single asset. Thus, failures in one indication could be perceived to have immediate read-through to others in the pipeline. Given the risks already

associated with transplant, continued safety of imlifidase in patients who in many cases are being treated with significant immunosuppressive regimens will be key. Although commercially available in Europe, imlifidase will need to have strong data in the ongoing Phase III study to support a U.S. approval and what we believe represents the larger commercial opportunity. Failures of clinical studies will have significant impact on Hansa's share price. Given the lack of acceptable surrogate markers in certain kidney diseases, long and expensive trials with renal outcome endpoints may be required for certain development programs.

Commercial Risk
Initial commercial launch of Idefirix in Europe has been slow to progress, as the company has worked through reimbursement governed separately across jurisdictions. Although we believe management has appropriately set investor expectations, the launch in Europe is likely to continue on a relatively steady trajectory in the near term. We believe the U.S. market represents the main value driver for Hansa, and thus, assuming positive results in ongoing clinical studies, commercial execution will be key to changing a treatment landscape that has had little by way of therapeutic innovation. This in itself has the potential to create inertia that the company will have to overcome to successfully commercialize imlifidase across a number of indications. Transplant practices can vary across geographies, and thus physician education on clinical data will be extremely important for commercial success.

Regulatory Risk
Like other biotechnology companies, Hansa is exposed to regulatory risks and must satisfy regulatory safety and efficacy criteria to gain approval. The ongoing ConfIdeS study to support U.S. approval has been specifically aligned with the FDA and should therefore meet requirements for approval. However, given the lack of innovation and drug development in the transplant space, regulatory risk is likely heightened by a lack of contemporary precedent for approvals. Similarly, outside of transplant, indications being pursued by Hansa have had little by way of innovative treatments developed over the last several decades, and standard-of-care practices tend to be down to physician experience, meaning decisions around appropriate comparators and endpoints could come with additional risk.

Competitive Risk
As discussed earlier in this report, competitive risk is likely lower than in many clinical development spaces, stemming from 1) the unique mechanism of action of imlifidase, meaning in some cases additional assets being developed could be complementary to, rather than directly competitive with, imlifidase, and 2) a general lack of clinical development in the diseases Hansa is pursuing with imlifidase. Although growing in the case of transplant, the markets Hansa pursues are relatively small, so there is less room for additional players, increasing the need for producing better efficacy than any emerging competition in order to be commercially viable.

Capital Risk
Given the broad clinical development program for imlifidase, we anticipate the company will require significant capital in the future for continued clinical development of its assets and any potential future commercialization. At the end of first quarter 2023, the company reported SEK 1.3 billion ($125 million) in cash and equivalents, which it believes provides funding into 2025. Changes in the competitive landscape, clinical setbacks, or continued macro pressures on the biotechnology space could hinder any future capital-raising capabilities for the company.

ESG Considerations

The biopharma industry is a resource-intensive field, generating hazardous waste and disposables from the manufacturing, preclinical stage, and clinical testing of therapies. Although many large biopharmaceutical companies have introduced plans to offset their carbon footprints, this is more challenging for smaller enterprises, but Hansa has acknowledged the importance of addressing this issue as it grows. Socially, Hansa is developing imlifidase as a means of broadening accessibility of transplant to a wider group of patients, and works with patient groups to expand access among ethnic and socio-economic groups who have faced access challenges in the past. The company also offers bridge financing to access imlifidase on a case-by-case basis to patients who have limited treatment options. From a responsibility perspective, Hansa highlights diligent selection criteria for new business partners and continued monitoring that these partners meet all regulations and laws, as well as the company's internal code of conduct. Like many companies in the biopharmaceutical space, discussions on drug pricing often come under scrutiny, and should Hansa be successful in the development of imlifidase in the U.S., differential pricing versus Europe is likely to be a focus given launch was initiated in Europe first.

Conclusion

Hansa Biopharma is developing a novel therapy capable of rapidly removing IgG antibodies that are driving immune diseases, including antibody-mediated rejection of kidney transplants, anti-GBM disease, and GBS. The therapy has conditional approval in Europe for the treatment of patients who are highly sensitized prior to kidney transplant, with potential approval in the United States in this indication in 2025, assuming positive results from the Phase III ConfIdeS trial. We believe the profile of imlifidase will continue to produce positive results across a number of indications, expanding the total market opportunity into potential blockbuster sales by 2027. Longer term, the company's next-generation approach in the NiceR program has the potential to allow for repeat administration and IgG reduction, which would drastically expand the potential indications for clinical development, driving additional upside for shareholders. We rate shares Outperform based on a fair value for imlifidase alone of SEK 160.

A timeline of expected events for Hansa Biopharma is shown in exhibit 31 and our current model and balance sheet are provided in exhibits 32 and 33.

Exhibit 31
Hansa Biopharma AB
Timeline

	Date	Product	Event
2023	1H	Imlifidase	Complete enrollment of Phase III ConfIdeS Phase III U.S. study in kidney transplantation
	1H	Imlifidase	First Patient Enrolled in Phase III anti-GBM Study
	2H	Imlifidase	Complete randomization in Phase III ConfIdeS Phase III U.S. study in kidney transplantation
	2H	Imlifidase	Full Results from Phase II Study in AMR
	2H	Imlifidase	Top-line data from Phase II GBS Study
	2H	Imlifidase	5-year Follow-up from Phase II Kidney Transplant Study
	2H	Imlifidase	Initiate clinical study of imlifidase as a pretreatment for gene therapy with Sarepta
2024	**1H**	**Imlifidase**	**U.S. kidney transplantation BLA submission**
	1H	Imlifidase	Comparative analysis of GBS Phase II to IGOS data

Source: Company reports

Exhibit 32
Hansa Biopharma AB
Income Statement
(currency in SEK in thousands except EPS and shares in thousands)

	2022A	Q1A	Q2E	Q3E	Q4E	2023E	2024E	2025E	2026E	2027E
Product Sales	86,735	14,306	24,169	42,295	54,378	134,170	306,353	527,978	890,013	1,471,752
Contract revenue, Axis Shield agreement	2,892	644	631	605	611	2,491	2,426	2,416	2,411	
Cost reimbursement, Axis Shield agreement	625	286	92	111	115	604	419	414	409	
Contract revenue, Sarepta, AskBio agreement	64,272	8,958	8,099	8,741	8,599	34,397	32,680	37,055	29,045	
Other Revenue	67,789	9,888	8,823	9,456	9,326	37,492	35,525	39,885	31,864	35,758
Total Revenue	154,525	24,194	32,992	51,751	63,703	171,663	341,879	567,863	921,877	1,507,510
COGS	38,477	9,646	3,625	6,344	8,157	27,772	45,953	89,310	177,754	293,965
SG&A	336,242	103,292	104,325	105,368	106,422	419,407	447,489	620,868	743,426	822,390
R&D	346,060	92,791	96,503	99,398	102,380	391,071	434,754	496,445	547,903	601,630
Other operating expenses (gain)	20,794	813								
Operating expenses	741,573	206,542	204,453	211,110	216,958	838,250	928,196	1,206,623	1,469,083	1,717,985
Operating income (loss)	(587,048)	(182,348)	(171,461)	(159,359)	(153,255)	(666,588)	(586,317)	(638,760)	(547,205)	(210,475)
Interest income (expense)	-21365	(22,717)	(23,931)	(24,648)	(19,521)	(90,817)	(99,147)	(109,616)	(101,405)	(83,515)
Net income (loss before tax)	(608,413)	(205,065)	(195,392)	(184,008)	(172,776)	(757,405)	(685,464)	(748,376)	(648,610)	(293,990)
Income tax (benefit)	1,155	356	375	353	331	1,415	1,314	1,435	1,246	567
Net income (loss) after tax	(609,568)	(205,421)	(195,767)	(184,361)	(173,107)	(758,820)	(686,778)	(749,811)	(649,856)	(294,558)
Net loss atributable to common shareholders	(609,568)	(205,421)	(195,767)	(184,361)	(173,107)	(758,820)	(686,778)	(749,811)	(649,856)	(294,558)
Earnings per share, basic	**(13.57)**	**(3.92)**	**(3.71)**	**(3.48)**	**(3.25)**	**(14.36)**	**(11.80)**	**(10.58)**	**(8.02)**	**(3.49)**
Earnings per share, diluted	**(13.57)**	**(3.92)**	**(3.71)**	**(3.48)**	**(3.25)**	**(14.36)**	**(11.80)**	**(10.58)**	**(8.02)**	**(3.49)**
Earnings per share, basic	**(1.30)**	**(0.38)**	**(0.36)**	**(0.33)**	**(0.31)**	**(1.38)**	**(1.13)**	**(1.02)**	**(0.77)**	**(0.34)**
Earnings per share, diluted	**(1.30)**	**(0.38)**	**(0.36)**	**(0.33)**	**(0.31)**	**(1.38)**	**(1.13)**	**(1.02)**	**(0.77)**	**(0.34)**
Weighted average common shares, basic	44,923	52,444	52,706	52,970	53,235	52,839	58,216	70,888	81,079	84,416
Weighted average common shares, diluted	44,923	52,444	52,706	52,970	53,235	52,839	58,216	70,888	81,079	84,416

Source: William Blair Equity Research

Exhibit 33
Hansa Biopharma AB
Balance Sheet
(currency in SEK in thousands except EPS and shares in thousands)

	2022A	Q1A	Q2E	Q3E	Q4E	2023E	2024E	2025E	2026E	2027E
Cash and Cash equivalents	1,493,936	1,286,820	1,095,105	916,531	759,661	759,661	1,202,305	2,957,554	2,148,692	1,524,677
Short-term investments	-	-	-	-	-	-	-	-	-	-
Trade receivables & contract assets	64,593	47,221	64,392	86,251	92,016	92,016	100,068	117,912	157,256	246,635
Inventories	973	1,037	390	682	877	877	1,470	4,349	5,915	9,353
Current receivables, non-interest bearing	42,959	58,346	58,346	58,346	58,346	58,346	58,346	58,346	58,346	58,346
Total current assets	1,602,461	1,393,424	1,218,233	1,061,811	910,900	910,900	1,362,190	3,138,161	2,370,209	1,839,011
Intangible assets	46,866	72,346	72,346	72,346	72,346	72,346	72,346	72,346	72,346	72,346
Property and Equipment	8,113	8,072	8,072	8,072	8,072	8,072	8,072	8,072	8,072	8,072
Leased Assets	27,723	25,845	25,845	25,845	25,845	25,845	25,845	25,845	25,845	25,845
Other	-	-	-	-	-	-	-	-	-	-
Total assets	1,685,163	1,499,687	1,324,496	1,168,074	1,017,163	1,017,163	1,468,453	3,244,424	2,476,472	1,945,274
Tax liability	604	757	757	757	757	757	757	757	757	757
Lease liabilities	7,165	7,211	7,211	7,211	7,211	7,211	7,211	7,211	7,211	7,211
Current liabilities, non-interest bearing	80,754	61,115	60,497	62,467	64,197	64,197	72,559	103,319	114,854	134,233
Deferred revenue	40,430	41,024	41,024	41,024	41,024	41,024	41,024	41,024	41,024	41,024
Contract Liabilities	27,013	34,986	34,986	34,986	34,986	34,986	34,986	34,986	34,986	34,986
Accrued expenses and other defferred income	108,747	95,809	94,840	97,928	100,641	100,641	138,272	196,889	218,870	255,800
Total current liabilities	264,713	240,902	239,315	244,373	248,816	248,816	294,810	384,186	417,702	474,011
Deffered tax liabilities	405	402	402	402	402	402	402	402	402	402
Provisions	5,192	5,109	5,109	5,109	5,109	5,109	5,109	5,109	5,109	5,109
Lease liabilities	21,326	19,512	17,744	15,976	14,208	14,208	7,136	64	-	-
Deferred revenue	29,500	20,625	20,625	20,625	20,625	20,625	20,625	20,625	20,625	20,625
Contingent consideration	757	786	786	786	786	786	786	786	786	786
Other long term liabilities	762,601	797,685	821,616	846,264	865,785	865,785	964,932	908,410	758,106	467,084
Total liabilities	1,084,494	1,085,021	1,105,596	1,133,535	1,155,731	1,155,731	1,293,800	1,319,581	1,202,731	968,017
Shareholders' equity	602,912	414,666	218,899	34,539	(138,568)	(138,568)	174,653	1,924,843	1,273,741	977,257
Total stockholders' equity	600,669	414,666	218,899	34,539	(138,568)	(138,568)	174,653	1,924,843	1,273,741	977,257

Source: William Blair Equity Research

The prices of the common stock of other public companies mentioned in this report follow:

Annexon Inc	$5.34
argenx SE (Outperform)	$185.23
AstraZeneca plc	$75.68
Morphosys Ag	$5.08
Rigel Pharmaceuticals Inc	$1.19
Sarepta Therapeutics Inc (Outperform)	$126.53
Selecta Biosciences (Not Rated)	$1.16

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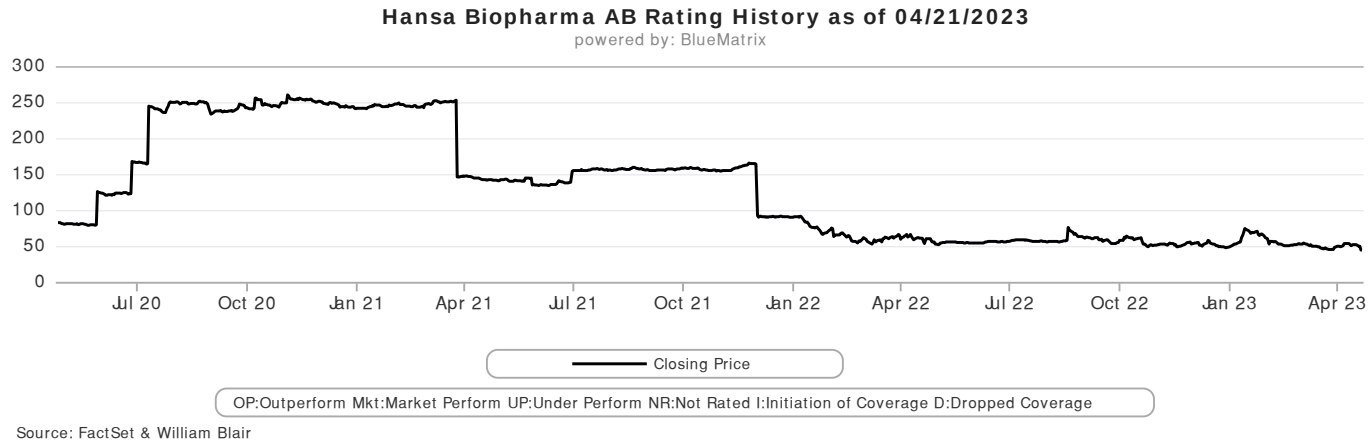
DOW JONES: 33809.00
S&P 500: 4133.52
NASDAQ: 12072.50



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Coverage Universe	Percent	Inv. Banking Relationships *	Percent
Outperform (Buy)	74	Outperform (Buy)	7
Market Perform (Hold)	26	Market Perform (Hold)	4
Underperform (Sell)	1	Underperform (Sell)	0

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